Irmeli Lindström

Men with asthma since youth

– Prognosis, impact of work and effect on work ability

Finnish Institute of Occupational Health

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CONTENTS

ABSTRACT

Asthma is a significant and increasing health problem among the working aged population and is associated with decreased work ability. The worsening of asthma due to conditions at work has been shown to be a common occurrence. The aim was to study the asthma prognosis and the work ability of men with asthma since youth. The first objective was to analyse the impact of individual characteristics and lung function tests at the age of around 20 as risk factors for current persistent asthma. The second aim was to assess work ability of men with asthma at 40 years of age and risk factors for decreased work ability. Finally, we investigated whether current work and workplace exposure is associated with asthma severity, asthma control and the occurrence of exacerbations at the age of 40.

We used the Finnish Defence Force registers to select the two different study populations. As our study populations consisted mainly of men with early-onset atopic asthma the results cannot be generalised to other types of asthma. Initially, in 2007 a postal questionnaire was sent to all 216 men with verified asthma from the 2004–2005 Central Military Hospital register. All study subjects included in our second study population were men currently aged at approximately 40 years old. The *Recruits with asthma* (Asthma Group 1, n=505) consisted of all asthmatics who were referred to the Central Military Hospital during the period 1987–1990 and who had relatively mild asthma in youth. The *Asthmatics exempted from service* (Asthma Group 2, n=393) included men who were exempted from military service during the period 1986–1989 due to asthma and had more severe asthma in youth. The *Controls* (n=1500) had performed their military service without asthma. A postal questionnaire including validated questions about asthma and work ability was sent out approximately twenty years after military service or exemption

at call-up. Thereafter, a total of 119 respondents from the *recruits with asthma* group attended the clinical tests.

Asthma was significantly less severe at the two-year follow-up than during military service (p=0.036) and allergic sensitisation was the most important determinant of more severe asthma. Approximately half of those men who belonged to our second study population and attended the clinical visit approximately twenty years after their military service had current persistent asthma. A positive exercise test and obstructive spirometry at baseline were associated with asthma persistence at the twenty-year follow-up. The self-assessed current work ability compared with life time best for *recruits with asthma* and *asthmatics exempted from service* was significantly reduced when compared with the *controls* (the adjusted odds ratio, (OR) 1.5, 95% confidence interval (95%CI) 1.0–2.2 and 1.6, 95%CI 1.0–2.5, respectively). Among the asthmatics being a current smoker, having only basic education, being a manual worker or being self-employed and suffering from current severe asthma were associated most strongly with decreased self-assessed work ability. In *asthmatics exempted from service,* being a manual worker or self-employed were also associated significantly with the occurrence of asthma exacerbations during past 12 months (adjusted OR 4.5, 95%CI 1.2–16.3).

Conclusions: Military aggravated asthma has a good short-term and long-term prognosis. A positive exercise test and obstructive spirometry might be clinically meaningful prognostic measures in males with asthma that began at a young age. Both mild and more severe asthma at the age of around 20 seems to be associated with reduced self-assessed work ability in 40-year-old men. Current work and occupational exposure may be associated with the occurrence of asthma exacerbations in middle-aged men who had relatively severe asthma at around 20 years of age. Occupational health care professionals and other health care providers should, therefore, follow carefully men with asthma that began in youth, supporting their work ability and paying close attention to their work environment.

TIIVISTELMÄ

Astma on yleinen sairaus työikäisessä väestössä, ja sen on osoitettu liittyvän alentuneeseen työkykyyn. Työn arvioidaan vaikeuttavan astmaoireita merkittävällä osalla työssä käyvistä astmaa sairastavista. Tämän väitöskirjatyön tarkoituksena oli selvittää astman ennustetta ja sairauden vaikutusta työkykyyn miehillä, jotka ovat sairastaneet astmaa nuoruudesta alkaen. Tarkempina tavoitteina oli tutkia keuhkojen toimintakokeiden ja allergiatutkimusten tulosten merkitystä pysyvän astman kehittymiseen. Toisena tavoitteena oli arvioida astmaa sairastavien miesten työkykyä noin 40 vuoden iässä ja riskitekijöitä, jotka liittyivät heikentyneeseen työkykyyn. Kolmanneksi selvitimme nykyisen työn ja työssä tapahtuvan altistumisen yhteyttä tämänhetkiseen astman vaikeusasteeseen, hoitotasapainoon ja pahenemisvaiheiden esiintymiseen.

Käytimme tutkimuksessamme kahta eri tutkimusaineistoa, jotka valittiin Puolustusvoimien rekistereistä. Koska tutkimusaineistoomme kuului lähinnä miehiä, joilla oli varhaisessa iässä alkava allerginen astma, tuloksiamme ei voi yleistää koskemaan muita astman fenotyyppejä. Aluksi selvitimme astman 2-vuotisennustetta varusmiespalveluksen jälkeen postikyselyn avulla ja valitsimme tähän tutkimukseen kaikki ne miehet, joita oli hoidettu Keskussotilassairaalassa astman vuoksi vuosina 2004–2005. Selvitimme astman pidempiaikaista ennustetta käyttäen toista tutkimusaineistoa. Siihen kuului kolme eri ryhmää ja kaikki tutkimukseen valitut miehet olivat parhaillaan noin 40 vuoden iässä. *Astmaa sairastavien varusmiesten* ryhmään (astma ryhmä 1, n = 505) valittiin kaikki varusmiehet, joita oli hoidettu Keskussotilassairaalassa vuosina 1987–1990 astman vuoksi. Nämä miehet edustivat nuoruudessaan lievää tai keskivaikeaa astmaa sairastavia. *Palveluksesta vapautettujen* ryhmään (astma ryhmä 2, n = 393) valittiin ne miehet, jotka oli vapautettu varusmiespalveluksesta astman vuoksi vuosina 1986–1989, ja tämä ryhmä

edusti nuoruudessaan melko vaikeaa astmaa sairastavia. *Verrokkiryhmään* (n = 1 500) valittiin satunnaisotoksella miehiä, jotka eivät sairastaneet astmaa varusmiespalveluksen aikana. Noin 20 vuotta varusmiespalveluksen jälkeen lähetimme postikyselyn, jossa esitettiin astmaa ja työkykyä koskevia kysymyksiä. Tämän jälkeen tehtyihin kliinisiin tutkimuksiin osallistui 119 miestä, jotka kuuluivat *astmaa sairastavien varusmiesten* ryhmään.

Kyselyn perusteella astma oli merkitsevästi lievempi kaksi vuotta varusmiespalveluksen jälkeen kuin sen aikana ($p = 0.036$), ja allergia oli tärkein vaikeampaa astmaa ennustava tekijä. Astman pidempiaikaista ennustetta selvittävässä tutkimuksessa noin puolet kliinisiin tutkimuksiin osallistuneista miehistä sairasti pysyvää astmaa 20 vuotta varusmiespalveluksen jälkeen. Positiivinen juoksurasituskoe ja obstruktiivinen spirometria varusmiesiässä liittyivät pysyvään astmaan 20 vuoden kuluttua. Tutkittavien omaan arvioon perustuva työkyky verrattuna elinaikaiseen parhaimpaan oli alentunut sekä *astmaa sairastavien varusmiesten* ryhmässä että *palveluksesta vapautettujen* ryhmässä verrattuna verrokkeihin (vakioitu odds ratio (OR) 1.5, 95 %:n luottamusväli, confidence interval (CI) 1.0–2.2 ja OR 1.6, 95 %CI 1.0–2.5, vastaavasti). Astmaa sairastavilla nykyinen tupakointi, ainoastaan peruskoulutus, työntekijänä (käsittää lähinnä tuotanto- ja palvelutyöntekijät) tai yrittäjänä toimiminen sekä tämänhetkinen vaikea astma liittyivät kaikkein selvimmin alentuneeseen työkykyyn. *Palveluksesta vapautettujen* ryhmässä työntekijänä tai yrittäjänä toimiminen liittyivät astman pahenemisvaiheen esiintymiseen viimeisen vuoden aikana (vakioitu OR 4.5, 95%CI 1.2–16.3).

Johtopäätökset: Varusmiespalveluksen aikana vaikeutuneella astmalla on hyvä lyhyt- ja pitkäaikaisennuste. Positiivinen juoksurasituskoe ja obstruktiivinen spirometria nuoruudessa saattavat olla kliinisesti merkittäviä astman ennusteeseen vaikuttavia tekijöitä. Sekä lievää ja että vaikeampaa astmaa nuoruudessaan sairastavien miesten omaan arvioon perustuva työkyky on alentunut noin 40 vuoden iässä. Nykyinen työ ja työperäinen altistuminen saattavat liittyä astman pahenemisvaiheiden esiintymiseen keski-ikäisillä miehillä, joilla oli ollut suhteellisen vaikea astma nuoruudessaan. Tämän vuoksi työterveyshuollossa ja muualla terveydenhuollossa olisi tärkeää seurata erityisen hyvin nuorena astmaan sairastuneita, tukea heidän työkykyään ja kiinnittää huomiota heidän työympäristöönsä.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to by their Roman numerals:

I Lindström I, Koponen P, Luukkonen R, Pallasaho P, Kauppi P, Latvala J, Karjalainen A and Lauerma A: Military service-aggravated asthma improves at two-year follow-up. Respiratory Medicine 2009; 103(12):1926–35

II Lindström I, Suojalehto H, Lindholm H, Pallasaho P, Luukkonen R, Karjalainen J, Lauerma A and Karjalainen A: Positive exercise test and obstructive spirometry in young male conscripts associated with persistent asthma 20 years later. Journal of Asthma 2012; 49(10):1051–1059

III Lindström I, Pallasaho P, Luukkonen R, Suojalehto H, Karjalainen J, Lauerma A and Karjalainen A: Reduced work ability in middle-aged men with asthma from youth – a 20-year follow-up. Respiratory Medicine 2011; 105(6):950–955

IV Lindström I, Suojalehto H, Lindholm H, Pallasaho P, Luukkonen R, Karjalainen J, Lauerma A and Karjalainen A: Middle-aged men with asthma since youth – the impact of work on asthma. Journal of Occupational and Environmental Medicine; in press

ABBREVIATIONS

ACT	Asthma control test
ATS	American Thoracic Society
BMI	Body mass index
CI	Confidence interval
ECRHS	European Community Respiratory Health Survey
$FEF_{25–75\%}$	Mean forced expiratory flow between 25 and 75% of the FVC
$FEF_{50\%}$	Forced expiratory flow rate at 50% of vital capacity
FENO	Fractional exhaled nitric oxide measurement
FEV_1	Forced expiratory volume in one second
FROD	Finnish Register of Occupational Disease
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
HMW	High molecular weight agent
HR	Hazard ratio
HWE	Healthy worker effect
ICS	Inhaled corticosteroids
ISCO	International classification of occupations
JEM	Job exposure matrix
LMW	Low molecular weight agent
OA	Occupational asthma
OR	Odds ratio
PAF	Population attributable factor
PEF	Peak expiratory flow
PRR	Prevalence rate ratio
RR	Risk ratio
SIC	Specific inhalation challenge
VGDF	Vapors, gases, dust, or fumes
WEA	Work exacerbated asthma

1 INTRODUCTION

Asthma is a significant health problem in the working-age population. Asthma incidence has been increasing during recent decades and no clear signs of levelling off can yet be detected (Anandan et al. 2010). The prevalence of asthma and asthma symptoms has increased especially in children and adolescents (Lai et al. 2009). A recent Finnish study reported a 9.4% asthma prevalence in adult Finnish population (Pallasaho et al. 2011). Thus one can conclude that currently and in future a significant proportion of workers have asthma and need to cope with asthma during their career.

Over the past decades, work-related asthma has increasingly been recognised as a public health concern due to its high prevalence. According to the most recent systematic analysis approximately 18% of adult-onset asthma is estimated to be caused by occupational exposures (Toren et al. 2009a). In addition to being a cause of asthma, work can also aggravate pre-existing or new-onset asthma and approximately 20% of working asthmatics are suggested to have work aggravated asthma (Henneberger et al. 2011). Based on several earlier studies, there seems to be consensus that asthma is associated with decreased work ability. However, only a few longitudinal studies exist regarding the effect of asthma on work ability (Toren et al. 2009b).

Identifying several clinically and inflammatory different asthma phenotypes and their presentations in different population groups has recently increased the awareness of the variable characteristics of asthma (Pavord 2012). At population level most asthmatics have mild form of the disease, although an estimation of 5–10% proportion of severe asthma exists (Holgate et al. 2006). The distribution of asthma severity is, however, dependent on the population studied. Additionally,

the treatment options for asthma have evolved markedly during recent decades. In Finland inhaled corticosteroids have been extensively used as first line therapy for persistent asthma since the 1980's and the National Asthma Programme has the aim of teaching primary care providers in the diagnosis and treatment of asthma (Haahtela et al. 2006).

It can be assumed that most asthmatics currently have a relatively mild form of the disease with good treatment options which might only have a minor effect on work ability. Additionally asthma treatment can potentially keep the disease stable in most cases despite exposure to irritants or asthmogens at work. This is likely to be especially true for asthma starting in childhood, because it is usually the atopic phenotype and generally milder than non-atopic adult-onset asthma (Moore et al. 2010). The Finnish Allergy Program encourages young people with severe asthma to avoid occupations with exposure to respiratory irritants, but generally, work as a fire fighter is the only explicit career restriction to those with mild asthma (Haahtela et al. 2012). There is a need for longitudinal studies about the effects of work on asthma starting at a young age in order to achieve evidence for vocational guidance for young asthmatics.

The present series of studies aimed to examine the prognosis and prognostic factors of asthma in men with asthma since childhood or early adulthood presenting mostly the early onset atopic asthma -phenotype. The more specific goals were to investigate work ability and the risk factors for decreased work ability as well as the associations between occupational exposure and asthma outcome. Recognising the modifiable risk factors of poor asthma outcome is important for decreasing the burden of asthma.

2 LITERATURE REVIEW

2.1 Asthma

2.1.1 Definition

Asthma is a complex disorder with many distinct clinical phenotypes, which manifest in interaction of genetic predisposition and environmental exposures. Until the 1980s bronchospasm was considered to be a key feature of asthma, but after that the increasing knowledge of airway inflammation has changed the definition of asthma. The current Global Initiative for Asthma (GINA) –report states that "Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment" (GINA 2012).

2.1.2 Pathogenesis of asthma

The key feature in asthma is a variable airway inflammation including many different types of inflammatory cells and mediators (GINA 2012). Cytokines, chemokines, cysteinyl leukotrienes, histamine, nitric oxide and prostaglandinD_2 are identified to be important mediators of asthmatic inflammation. Airway inflammation leads to several pathophysiological changes in airways typical for asthma, like thickening of the basement membrane, hypertrophy and hyperplasia of smooth muscle cells, blood vessel proliferation and increased number of goblet cells.

These changes are usually described as airway remodelling and can result to irreversible narrowing of the airways.

Asthmatic airway inflammation has been referred to be as eosinophilic inflammation, but during last two decades the awareness of the complex and variable nature of this inflammation has increased (Gibson 2009). Recently asthmatic inflammation has often been studied non-invasively using induced sputum samples. In healthy subjects, the cell count of these samples consists of approximately 2/3 of macrophages and 1/3 neutrophils without the presence of significant numbers of eosinophils or lymphocytes. In asthmatics the following inflammatory cell profiles have been identified: 1) eosinophilic, 2) neutrophilic or non-eosinophilic, 3) mixed granulocytic, and 4) paucigranulocytic; with normal levels of neutrophils and absent eosinophils (Haldar et al. 2007). As many as 25% of untreated symptomatic asthmatics (Green et al. 2002a) and 50% of those treated with high-dose inhaled corticosteroids (ICS) had a normal sputum eosinophil count (Gibson et al. 2001). In a recent study of 508 asthmatics from the University Asthma Clinic 42% had eosinophilic, 16% neutrophilic, 3% mixed granulocytic and 40% paucigranulocytic inflammation and use of ICS showed not significant effect on the inflammation types (Schleich et al. 2013).

Eosinophilia is typically found in a classic atopic type of asthma with IgE-mediated sensitisation and most of these patients have a good response to ICS therapy (Pavord 2012). Neutrophilic inflammation in asthmatics has been connected to obesity (Haldar et al. 2007), smoking (Chalmers et al. 2001) and exposure to occupational low-molecular-weight sensitizers (Anees et al. 2002), as well as to older age, female gender and poor response to ICS (Green et al. 2002a). Asthmatic patients with mixed granulocytic inflammation have been shown to have lowest lung function, increased daily symptoms and increased health care use (Hastie et al. 2010), while those with paucigranulocytic inflammation typically have well-controlled or intermittent disease (Haldar et al. 2007). The clinical phenotypes taking account inflammatory profiles from cluster approaches are described in chapter 2.1.4.

2.1.3 Clinical examinations in asthma

Symptoms and clinical signs

The typical asthma symptoms are intermittent wheezing, chest tightness, shortness of breath, coughing and mucus production. The variability of these symptoms, their precipitation by factors such as exercise, cold air, allergens, viral respiratory infections or specific agents such as aspirin, form the basis of the clinical diagnosis of asthma. Furthermore the symptom relief using bronchodilators and ICS is characteristic to asthma (Asthma: Current Care guideline, 2012), although phenotypes with a poor response to conventional asthma therapies have been identified (Haldar et al. 2008). Patients with cough-variant asthma have a cough as the principal, if not only, asthma symptom and have typically more symptoms at night (Johnson et al. 1991).

Due to the variable characteristics of asthma, a physical examination of the respiratory system may be normal. The most usual abnormal finding is expiratory wheezing on lung auscultation, which however is sometimes detected only in forced expiration. In severe obstruction wheezing is sometimes missing, because of severely reduced air flow and ventilation (GINA 2012).

Measurements of lung function

Spirometry is a physical test that measures how an individual inhales or exhales volumes of air as a function of time (Miller et al. 2005). The primary signal measured in spirometry may be volume or flow and several international guidelines have been created for conducting the measurements (American Thoracic Society (ATS) 1987; ATS 1995; Miller et al. 2005). The variation of normal values in spirometry is large and the predicted values appropriate to the patient's ethnic group, sex, age and height should be used. The predicted values of Viljanen are used for the adult subjects of Finnish origin (Viljanen 1982).

The most important parameters used and expressed in litres are: 1) forced vital capacity (FVC), the maximum volume of air exhaled with maximum forced effort from maximum inhalation and 2) forced expiratory volume in 1 second (FEV_1), the maximum volume of air exhaled in the first second of forced expiration from a position of full inhalation.

The most useful assessment of airflow limitation is the ratio of FEV_1 to FVC, which is normally 0.75–0.80 and can be 0.90 in children. The spirometric parameters mentioned above are usually expressed as absolute values and as a percentage of the predictive values. Spirometry is the recommended method of measuring airflow limitation and reversibility to establish a diagnosis of asthma (GINA 2012, Asthma: Current Care guideline, 2012). The term reversibility is generally applied to rapid improvements in FEV_1 measured within minutes after inhalation of rapid-acting bronchodilatator for example salbutamol 200–400μg.

Mean forced expiratory flow between 25 and 75% of the FVC ($FEF_{25–75\%}$) and forced expiratory flow rate at 50% of vital capacity ($FEF_{50\%}$) are the spirometric variables most commonly cited as indicators of small airways obstruction, although they have been criticised as having a marked measurement variability and poor correlation with other measures of air trapping (Sorkness et al. 2008), which is an important feature observed in small airway disease. The other methods used to detect small airways obstruction include impulse oscillometry, nitrogen washout test, bronchoscopy, sputum induction, fractional exhaled nitric oxide and high-resolution computed tomography (van der Wiel et al. 2013).

Peak Expiratory Flow (PEF)-monitoring is performed by using a portable meter in a home setting in order to measure day-to-day variability of airflow limitation. The measurements are done first after waking in the morning, when values are typically at their lowest, and in the evening. Usually the measurements are also taken before and few minutes after bronchodilatator medication. The diurnal variation can be defined as the difference between daily maximum and minimum values expressed as % of the daily mean value (GINA 2012).

Airway hyperresponsiveness

Airway hyperresponsiveness is a major pathophysiological feature of asthma and can be defined as "an increase in the ease and degree of airway narrowing to inhaled bronchoconstrictor stimuli of chemical and physical origin, leading to variability in airway obstruction" (Sterk et al. 1993). Bronchoconstrictor stimuli are classified according to the main mechanism through which they induce airway limitation. Direct stimuli such as histamine and methacholine act directly on bronchial smooth

muscle, while indirect stimuli such as exercise, mannitol or eucapnic hyperventilation induce the release of bronchoconstriction mediators from inflammatory cells (Sterk et al. 1993). The pathophysiology of airways hyperresponsiveness measured with these two methods differs. In the direct bronchial provocation test the response is suggested to be dependent on both underlying inflammation and/or presence of airway remodelling; while in the indirect bronchial provocation test the presence of inflammation (e.g. eosinophils, mast cells) is a key feature for the response (Brannan et al. 2012). In steroid-naïve asthma patients the response to indirect stimuli has been connected to markers of eosinophilic inflammation; increased levels of sputum eosinophilia and fractional exhaled nitric oxide measurements (FENO) (Porsbjerg et al. 2008). Therefore it has been postulated that airway hyperresponsiveness to indirect stimuli could be used to identify asthma patients benefitting from ICS therapy (Brannan et al. 2012). This has been supported by the impairment of mannitol induced hyperreactivity and asthma symptoms during ICS therapy (Brannan et al. 2002; Koskela et al. 2003).

The direct challenge test has been shown to be more sensitive and less specific in diagnosing asthma when compared with the indirect challenge test (Cockcroft 2010). Additionally the positive predictive value of metacholine challenge in diagnosing asthma has been shown to increase as the degree of airways hyperresponsiveness is greater (e.g. the provocative dose of metacholine causing a 20% fall in FEV_1 is lower). However airway hyperresponsiveness is not specific to asthma and up to 70% of subjects with airway hyperresponsiveness have been found to be without respiratory symptoms (Kolnaar et al. 1997).

Measuring airway inflammation

The non-invasive methods used to measure airway inflammation in asthma are FENO and examination of spontaneously produced or hypertonic-saline induced sputum analysis. Levels of exhaled nitric oxide have shown to be elevated in people with untreated asthma compared to non-asthmatic subjects and sputum analyses have shown eosinophilic or neutrophilic inflammation in asthmatics. Although these findings are not specific to asthma both FENO and sputum analysis can be useful in evaluating the optimal treatment for asthma (Green et al. 2002b; Smith et al. 2005).

Establishing asthma diagnosis

Despite the important role of airway inflammation in asthma pathogenesis and treatment, according to current international (GINA 2012) and the Finnish national guidelines (Asthma: Current Care guideline, 2012) the diagnosis of asthma is based on observing reversible airflow obstruction. According to GINA guidelines the diagnosis of asthma can be confirmed in patients having typical symptoms by demonstrating: 1) the improvement of ≥ 12% and 200ml in FEV1 in response to brochodilator in spirometry, 2) the improvement of ≥ 20% and 60l/min in PEF in response to bronchodilator or diurnal variation ≥ 20% in PEF or 3) showing hyperresponsiveness in direct or indirect airway challenges.

2.1.4 Classification

Phenotypes

There is increasing awareness of heterogeneity of asthma and also the overlapping of asthma with chronic bronchitis and emphysema (Weatherall et al. 2009). Recent reviews have highlighted the importance of different asthma phenotypes, their natural history and varying treatment responses (Wenzel 2006). Allergic and non-allergic asthma are probably the most common discussed phenotypes. The former means asthma related to atopy e.g. presence of positive skin prick tests or the clinical response to common environmental allergens, while nonallergic asthma manifests without atopy. Other phenotypes have been defined by clinical or physiological categories (i.e. severity, age of onset and chronic airflow obstruction), asthma triggers (i.e. exercise, allergens, occupational allergens and irritants) or the type of inflammation (eosinophilic or neutrophilic asthma) (Wenzel 2006). Due to the variability of asthma, these phenotypes may not be enough to classify asthma. In a recent adult study the populations of two large epidemiological studies were included and using a clustering approach four different phenotypes were identified "active treated allergic childhood-onset asthma", "active treated adult-onset asthma", "inactive/mild untreated allergic asthma" and "inactive/mild untreated non-allergic asthma" (Siroux et al. 2011).

The pattern of granulocyte inflammation in induced sputum samples combined with clinical features can be used to identify different inflam-

matory phenotypes of asthma (Pavord 2012). This type of characterization seems to be relevant due to the increasing evidence of different treatment responses of these phenotypes (Green et al. 2002a). Using cluster analyses Haldar et al (Haldar et al. 2008) identified in study populations of primary and secondary care five different phenotypes: "early symptom predominant", "obese female non-eosinophilic", "early onset atopic asthma", "benign asthma" and "inflammation predominant". "Early symptom dominant" and "obese female non-eosinophilic" asthma had high symptom expression but little evidence of eosinophilic inflammation; therefore consideration of down titration of ICS was suggested. In contrast "early onset atopic" and "benign asthma" phenotypes showed concordance between symptoms, inflammation and lung function and the authors suggested symptom based treatment titration to be probably suitable. Patients with "inflammation predominant" asthma tended to be males and had high prevalence of rhinosinusitis, nasal polyps, aspirin sensitivity and despite prominent eosinophilic inflammation relatively few symptoms. The targeting of corticosteroids by monitoring inflammation was thought be useful.

In severe disease with poor treatment response the distinction between asthma and COPD can be challenging because of shared causal factors. Therefore, the suggestion of moving the focus from diagnostic labelling to the analysis of main mechanism and individual phenotype in order to find most effective phenotype-specific treatment exists (Pavord 2012).

Severity

The definition of asthma severity has evolved during recent years (Taylor et al. 2008a). In the severity evaluation it is important to include both the severity of underlying disease and its response to treatment. Asthma severity is not a static phenomenon, but can change over months and years. Asthma severity may be influenced by the underlying disease activity and by the asthma phenotype.

In the 1995 GINA guidelines, overall asthma severity was assessed on the basis of the patient's clinical characteristics prior to commencing therapy (GINA 1995). The 2002 version of the GINA guidelines classified asthma relying on three dimensions: 1) perceived symptoms, 2) lung function and 3) type of asthma treatment (Global Intiative for

Asthma (GINA) 2002). In this classification the clinical severity is classified in 1 of 4 steps according to the frequency of nocturnal and diurnal symptoms and FEV_1% predicted. Treatment is classified in 1 of 4 steps according to the reported daily medication use. Final asthma severity is a composition of these two independent classifications. The following categories were used: intermittent, mild persistent, moderate persistent and severe persistent.

According to the current GINA guidelines asthma severity is classified on the basis of intensity of treatment required to achieve good asthma control (GINA 2012). Mild asthma is asthma that can be well controlled with low-dose inhaled corticosteroids or leucotriene modifiers or chromones. Severe asthma is asthma that requires high intensity treatment to maintain good control or where good control is not achieved despite of high intensity treatment. This classification suits poorly to population based studies, where a portion of the asthmatics are untreated, undertreated or overtreated. Additionally asthma severity is highly dependent on the steroid response, which is usually poor in neutrophilic asthma (Green et al. 2002a). It has been postulated, that when phenotype-specific treatment becomes available some asthmatics currently classified as having severe disease might be changed to the mild asthma category (GINA 2012).

In a Swedish study multi-symptom asthma was defined as having reported physician-diagnosed asthma, use of asthma medication, recurrent wheeze, attacks of shortness of breath and at least one additional respiratory symptom (Ekerljung et al. 2011). As multi-symptom asthma was related to signs of more severe disease – lower FEV_1% predicted higher FENO and more pronounced hyperresponsiveness – it was suggested as a useful epidemiological marker of asthma severity. Eisner et al validated another score called the severity of asthma score, which is based on a validated disease-specific questionnaire that addresses frequency of asthma symptoms, use of systemic corticosteroids, use of other asthma medications, and history of hospitalisation/intubation for asthma (Eisner et al. 2012). The severity score of asthma demonstrated an ability to predict asthma exacerbations better than the asthma control test (ACT) and FEV_1 in moderate to severe asthma for example.

Control

The 1995 GINA guidelines already introduced the concept of the medication required to maintain control (GINA 1995). This was further developed by Cockcroft and Swystun, who established asthma severity by the minimum treatment required to maintain asthma control (Cockcroft et al. 1996). The aim of asthma medication is to achieve and maintain control for prolonged periods. Assessment of asthma control should incorporate both current clinical control (e.g. symptoms, reliever use and lung function) and future risk (e.g. exacerbations, lung function decline and side-effects of medication) (Taylor et al. 2008a; Reddel et al. 2009; GINA 2012).

However there is no golden standard in the measurement of asthma control (Reddel et al. 2009). According to current GINA classification, subjects having daytime symptoms less than three times a week and/or need of rescue medication, no nocturnal symptoms or limitation of activities and PEF/FEV_1 ≥ 80% or personal best are considered to have currently clinically controlled asthma (GINA 2012). Asthma is considered to be partly controlled if 1 or 2 of the above features are absent and uncontrolled if more than 2 features are absent. Assessment of current asthma control should preferably be conducted over a four week period.

Several validated self-administered questionnaires are available to measure current asthma control. ACT is a widely used questionnaire, which assesses key components of asthma control over the previous 4 weeks with five items: shortness of breath, interference of activity, use of rescue medications, night time awakenings and patient rating of asthma control (Nathan et al. 2004). The ACT scale ranges from 5 to 25, with higher scores indicating better asthma control and subjects scoring less than 20 are considered to have poorly controlled asthma. The ACT has been validated against specialist rating of asthma control and spirometry (Nathan et al. 2004; Schatz et al. 2006). The ACT result cannot, however, been changed directly to GINA guidelines based asthma control classification. The Asthma Therapy Assessment Questionnaire is a four-item questionnaire about asthma symptoms during the previous 4 weeks (Vollmer et al. 1999). In the Asthma Control Questionnaire, FEV_1% predicted is included in a six-item questionnaire about asthma symptoms during the previous week (Juniper et al. 1999). The Asthma Control Scoring

System includes FEV_1 values and induced sputum eosinophilic count in addition to asthma symptoms, use of rescue medication and effects on activities in the evaluation of asthma control (Boulet et al. 2002).

2.1.5 Asthma medication

Based on the current international (GINA 2012) and Finnish guidelines (Asthma: Current Care guideline, 2012) the goal of asthma treatment is to achieve and maintain clinical control. Based on GINA 2012 the treatment is increased or decreased in steps and can be divided into *controllers* (ICS, oral corticosteroids, leukotriene modifiers, long-acting β_2–agonists, theophylline, cromones and anti-IgE) and *relievers* (short acting β_2–agonists and inhaled anticholinergics). Finnish guidelines include long-acting anticholinergics to the controllers in adults, while cromones are not included. ICS are the most effective controller therapy and they are recommended to be used on daily bases in persistent asthma, although some subjects with mild disease might achieve good control with leukotriene modifiers. ICS has shown to be effective in reducing asthma symptoms, decreasing airway hyperresponsiveness, controlling airway inflammation and reducing exacerbations (Juniper et al. 1990). Improved deposition of ICS to peripheral airways is achieved with new small particle size inhalers, which are theoretically benefitting patients with evidence of small airway disease (Barnes 2012).

Based on GINA 2012 if asthma is poorly controlled with a low dose of ICS another controller medication, usually leukotriene modifier or long-acting β_2–agonists, is added or the dose of ICS is increased to a moderate level. In the next step a third controller therapy is added or the dose of ICS is increased to a high level. A low dose of oral corticosteroids is recommended regularly, if asthma is severely uncontrolled with high dose ICS in combination with several other control therapies. Anti-IgE is a novel therapy for severe allergic asthma patients with high-level serum total IgE and uncontrolled disease on ICS.

Recently the role of this "one-size-fits-all" type therapy has been debated (Pavord 2012). Pavord (2012) suggested that phenotype specific treatment, requiring evaluation of mechanisms of mortality, would be beneficial for patients with more complex disease. In neutrophilic asthma treatment approaches has not been investigated extensively, but aggressive

therapy with ICS is unlikely to be helpful (Green et al. 2002a). Simpson reported reduced neutrophilic inflammation and better quality of life in response to long-term macrolide antibiotics, although no effect on symptoms or lung function was detected (Simpson et al. 2008). Macrolides have an anti-inflammatory effect and several non-antibiotic macrolides are now in development (Barnes 2012). In addition several new mediator specific blockers, including IL-5, IL-13, IL-9, and prostaglandin D_2 are in clinical trials and might be beneficial to asthma patients.

2.2 Epidemiology in working age

2.2.1 Prevalence

Asthma is the most common chronic respiratory disease in the world and approximately 300 million people in the world currently have asthma (Bahadori et al. 2009). Lack of a golden standard for defining asthma in epidemiological studies makes the evaluation of asthma prevalence and incidence a challenge. As Anderson stated "The reliable assessment of the trend in asthma prevalence requires repeated cross-sectional studies on different occasions on the same population using the same methods to define asthma. Unfortunately only very few studies with these characteristics are available" (Anderson 2005).

In questionnaire studies, both questions about asthma symptoms and physician diagnosed asthma have been used, however the prevalence rates based on these data are highly dependent on the awareness of asthma in the population studied (Eder et al. 2006). In 1992, Toelle et al showed that a combination of bronchial hyperresponsiveness and recent wheezing (in the 12 months prior to study) identified subjects having more severe asthma and concluded this definition to be useful in measuring the prevalence of clinically important asthma in populations (Toelle et al. 1992). The question about physician-diagnosed asthma has yielded high specificity, but rather low sensitivity (mean 68%), when validated with clinically verified asthma (Toren et al. 1993). Airway hyperresponsiveness also has high specificity (about 80%), but low sensitivity (below 50%) (Peat et al. 2001). Questions on asthma related symptoms have been shown to attain a better combination of sensitivity and specificity (Pekkanen et al. 1999).

The prevalence of asthma increased worldwide in the second half of the last century until the 1990s, but since then there has been no clear temporal pattern (Eder et al. 2006). Some studies suggest a stabilising or even decreasing prevalence of asthma (Chinn et al. 2004; Lotvall et al. 2009), while others suggest that it is still increasing (Anandan et al. 2010; Gershon et al. 2010). The recent systematic review of epidemiological studies found no overall signs of reduction of asthma prevalence; on the contrary an increasing prevalence in many parts of the world was suggested (Anandan et al. 2010). However the utilisation of emergency healthcare is reported to be reduced in some economically developed countries, most probably due to an improvement in the quality of care. De Marco et al reported an increase in median prevalence of current asthma from 4.1% to 6.6% in Italian young adults in 1991–2010 (de Marco et al. 2012). The prevalence of asthma was stable during the nineties and increased from 1998–2000 to 2007–2010 mainly in subjects who did not report allergic rhinitis.

Asthma prevalence has increased in Finland during recent decades. In 1980, the prevalence of asthma was 4.1% in the urban population and 2.7% in the rural population (Heinonen et al. 1987). In 1996, a postal questionnaire survey performed in southern Finland showed a non-response adjusted asthma prevalence of 4.4% among adults aged 18–65 years (Hedman et al. 1999). The FinEsS study from northern Finland reported asthma prevalence of 6.0% in adults aged 20–69 years based on the question regarding physician-diagnosed asthma (Kotaniemi et al. 2002). In the same study, asthma prevalence was 6.8% in 1996 and 9.4% in 2007 in the Helsinki area (Pallasaho et al. 1999; Pallasaho et al. 2011).

Asthma prevalence among young Finnish men recruited to military service remained steady between 0.02% and 0.08% from 1926 to 1961, while from 1961 to 1989 20-fold increase was shown (Haahtela et al. 1990). Latvala et al showed a further increase with no signs levelling off and a prevalence of 3.45% was reached in 2003 (Latvala et al. 2005). By contrast, the trends of disabelling asthma turned downwards.

2.2.2 Incidence

The different definitions of asthma and different methods used make the comparison of incidence rates in different studies difficult. In the 16–50 years old Swedish general population the incidence rate was 1.1/1000/year (Toren et al. 1999a), while in the Danish twin study of young adults it was 5.5./1000/year (Thomsen et al. 2005). In the European Community Respiratory Health survey (ECRHS) 4588 young adults (20–44 years old) who were free from asthma at baseline in 1990–1995 were followed for 9 years (Anto et al. 2010). The incidence rate of new-onset asthma was 4.5 per 1000 person-years

Karjalainen et al reported incidence rates of 1.65/1000/year for men and 2.47/1000/year for women in Finland in a large follow-up cohort of nearly 50 000 incident cases of asthma in 1986–1998, which were identified from national registers for reimbursement of asthma medication and occupational diseases (Karjalainen et al. 2001). This compensation is given only to persons fulfilling strict diagnostic criteria, which probably has led to underestimation of real asthma incidence. In the FinEsS study inhabitants of Helsinki aged between 20 and 69 years were followed for 11 years with the questionnaire and the reported incidence rate ranged from 2.5 to 3.7/1000/year depending on how the population at risk was defined (Pallasaho et al. 2011).

2.2.3 Etiology

Asthma in working-age population may have persisted from childhood, may have occurred as a relapse of earlier childhood asthma or may be true adult-onset of asthma without symptoms in earlier life. Therefore etiological factors of both childhood-onset and adult-onset asthma need to be taken into account. Both host related factors (eg. genes, gender and obesity) and environmental factors influence the development of asthma in a complex and interactive way.

Host related factors

Family and twin studies have indicated that *genetics* plays an important role in the development of asthma and allergy, likely through several

genes of moderate effect (Willemsen et al. 2008). Although a positive family history predicts an increased risk of asthma, it has been shown only to identify a minority of children at risk (Burke et al. 2003). In the ECRHS, young adults reporting maternal asthma had 1.91-fold risk of new-onset asthma. (Anto et al. 2010).

Gender affects the development of asthma in time-dependent manner (Almqvist et al. 2008). Asthma is far more common in boys than girls during early childhood. The prevalence equalises between the genders during adolescence and then switches to a female predominance in adulthood. In a recent report by the ECRHS, the follow-up of young adults without asthma at baseline showed a higher incidence of asthma in women than in men (Odds ratio, OR 1.97, 95% Confidence interval, 95%CI 1.38–2.81) (Anto et al. 2010). *Atopy* is strongly associated with asthma, especially with asthma starting at a young age (Sears et al. 1991; Thomsen et al. 2006). The role of atopy seems more unclear in new-onset asthma in adults and the possible overestimation of its meaning has been argued (Pearce et al. 1999). In the ECRHS, only one in five cases of new-onset asthma was estimated to be attributable of atopy (Anto et al. 2010). *Allergic rhinitis* has shown to increase asthma risk in adults (Anto et al. 2010; Pallasaho et al. 2011), as well as *aspirin intolerance* and *nasal polyposis* (Hedman et al. 1999). In a recent study *chronic rhinosinusitis* without nasal allergies was associated with late-onset asthma (Jarvis et al. 2011). *Bronchial hyperresponsiveness* and FEV_1 < *100% predicted* increased significantly the risk of new-onset asthma in the ECRHS (Anto et al. 2010).

There is increasing evidence relating to subjects that are *overweight and obese* and the prevalence and incidence of asthma in both adults (Sin et al. 2008) and children (Chu et al. 2009), although most consistently in adolescent girls (Ho et al. 2011). It is considered to be unlikely that the association is attributable to a reverse causation – that is, asthma causes reduced physical exercise and weight gain (Schaub et al. 2005).

Environmental factors

Environmental factors play also important role in the development of asthma. According to a meta-analysis *parental smoking* is concluded to be very likely causally related to childhood asthma (Strachan et al.

1998). In another meta-analysis it was concluded that exposure to passive smoking increases the incidence of wheeze and asthma in children and young people by at least 20% and that particularly prenatal and postnatal maternal smoking is associated with increased asthma risk (Burke et al. 2012). A number of studies have also shown that *active smoking* is associated with the onset of asthma in adolescents and adults (Strachan et al. 1996; Withers et al. 1998; Piipari et al. 2004).

The exposure to evident *indoor moulds* or dampness in children and adults is associated with asthma onset and asthma exacerbations. The evidence of causal relationship is however lacking except for asthma exacerbations in children (Mendell et al. 2011). The relationship between exposure to *indoor and outdoor allergens* as well as *air pollution* and the asthma onset is unclear (Anto 2012). The role of occupational exposures is described in chapter 2.3

The role of *respiratory tract infections* in the development of asthma is still poorly understood (Rosenthal et al. 2010), although physicians have long recognised an association between common respiratory tract illnesses and the onset and worsening of wheeze and asthma.

The role of *diet* and particularly that of breast feeding in the onset of asthma has been widely studied. As the effect of breast feeding is mostly limited to early childhood wheezing disease, it is not referred to here. The evidence of a causal relationship between asthma and other dietary intake is still poor (McKeever et al. 2004; Eder et al. 2006). There is accumulating evidence that vitamin D deficiency is related to an increased risk of asthma, but on-going clinical trials need to show the protective effect of vitamin D supplementation on asthma prevalence (Paul et al. 2012). Interestingly, vitamin D sufficiency has also been associated with improved lung function in ICS treated children with asthma (Wu et al. 2012). A recent study demonstrated the association between prevalence of asthma, rhinoconjuctivitis and eczema symptoms and the consumption of fast food in children and adolescents (Ellwood et al. 2013).

2.2.4 Prognosis of asthma

The natural history of asthma is still poorly known and measuring asthma prognosis in a population-based framework is challenging and not well established. The methods used are the evaluation of asthma remission,

severity and control as well as occurrence of severe asthma and lung function measurements. The use of asthma medication, mortality, hospitalisation rate, emergency visits, doctor visits and work disability due to asthma have been used as markers of asthma prognosis for example in community-based educational programmes (Haahtela et al. 2006). The age at which patients with asthma die does not differ from the population as whole and death is usually caused by the same diseases as the general population (Silverstein et al. 1994). However older adults with asthma die of respiratory diseases more often than individuals in the general population.

Remission

There is no universally accepted definition for asthma remission. Most studies include the absence of respiratory symptoms and asthma medication use (De Marco et al. 2002), whereas others also include normal lung function and/or absence of airway hyperresponsiveness (Vonk et al. 2004; Spahn et al. 2008). The time period without asthma symptoms and asthma medication required for asthma remission has varied from one to three years in different studies (Ronmark et al. 1999; van den Toorn et al. 2001; Vonk et al. 2004; Spahn et al. 2008). Several different definitions of asthma remission used and different populations studied (children/young adults/older adults) may partly explain the varying results between studies on asthma remission. One can also argue that the basis of asthma diagnosis significantly affects the remission rates.

In unselected population-based or preselected cohorts the proportion of subjects with childhood asthma being in remission varies from 10–70% (Spahn et al. 2008). The longest longitudinal study of the natural history of asthma was completed in Australia using a 1957 birth cohort of 30 000 children. Only 30% of the children with an asthma diagnosis at the age of 7 years were free of wheezing at the age of 42 years (Phelan et al. 2002). Vonk et al followed a cohort of 119 children with asthma over a period of 30 years and found that 22% of the cohort was in complete remission and 30% in clinical remission (Vonk et al. 2004). The latter was defined as having no wheeze or asthma exacerbations or use of ICS during last three years. Normal lung function and absence of airways hyperresponsiveness were additional criteria for complete

remission. In another follow-up cohort of 613 children with wheezing at baseline, 25% were shown to be in remission at 26 years of age (Sears et al. 2003).

In a cross-sectional study of young Italian adults, remission was defined as no asthma attacks during the previous 2 years and no use of asthma drugs during the previous 12 months (De Marco et al. 2002). Overall 45.8% of the subjects were in remission (41.6% of women and 49.5% of men). In the RHINE study, the young adult population of Northern Europe was studied and a remission rate of 20.2 per 1000 person years was found, i.e. about 20% of the subjects recovered from their asthma during a 10-year period (Holm et al. 2007). In the Swedish population based study of middle-aged and older subjects, asthma remission during the 10 year period under study was only 6% (Ronmark et al. 1999).

Quitting smoking (Ronmark et al. 1999; Holm et al. 2007), having mild disease (Panhuysen et al. 1997; Ronmark et al. 1999; de Marco et al. 2006; Holm et al. 2007), shorter duration of disease (De Marco et al. 2002), and in children male sex (Sears et al. 2003) and normal lung function (Sears et al. 2003; Vonk et al. 2004) have been shown to predict asthma remission. In the studies of young adults, the earlier age of asthma onset has been associated with asthma remission (Panhuysen et al. 1997; De Marco et al. 2002) and a reverse association with change in body mass index, BMI has also been found (de Marco et al. 2006).

Asthma severity

As described earlier in chapter 2.1.4 the evaluation of asthma severity in population-based studies has been mainly based on different versions of GINA guidelines or self-made scores of specific researches.

In the first survey of ECRHS I asthma was classified as mild, moderate or severe based on score derived from Ronchetti (Ronchetti et al. 1997) and FEV_1 of predicted values (Zureik et al. 2002). Of the 1132 subjects 50% had mild asthma, 29% had moderate asthma and 21% had severe asthma. In the cross-sectional part of second survey about 30% of subjects suffered from moderate-to-severe asthma (Cazzoletti et al. 2010). In the prospective part of second survey (ECRHS II) 856 young adults having asthma were followed for 9 years and then asthma

severity was evaluated based on the 2002 GINA classification (GINA 2002). At the end of the follow-up 11.9% of the subjects were in remission (no symptoms, no exacerbations, no asthma medications in the last year), and 45.3% had intermittent, 8.1% had mild persistent, 16.7% moderate persistent and 18.0% severe persistent asthma (de Marco et al. 2006). The similar distribution of asthma severity has also been reported by other authors (Porpodis et al. 2009).

In the cross-sectional ECRHS I and II studies sensitisation to moulds (*Alternaria alternata or Cladosporium herbarum)* associated with severe asthma (Zureik et al. 2002; Cazzoletti et al. 2010). Associations between persistent asthma and sensitization to house dust mite, nonseasonal asthma, an older age at asthma onset, and chronic cough and phlegm were also reported, while sensitisation to cat was related to severe asthma only (Cazzoletti et al. 2010). In the prospective part of ECRHS II participants with moderate or severe persistent asthma at follow-up were compared with those having intermittent asthma. Poorer FEV_1% predicted, a poorer symptom control, higher IgE levels and a higher prevalence of chronic cough/mucus hypersecretion at baseline predicted moderate or severe persistent asthma (de Marco et al. 2006). No gender difference in asthma severity has been found in ECRHs studies (Raherison et al. 2009).

In birth cohort studies smoking, airway hyperresponsiveness, female sex, atopy and a decreased FEV_1/FVC ratio in young adults predict persistence of asthma in older age (Sears et al. 2003; Taylor et al. 2005). In a Swedish study the prevalence of multi-symptom asthma was 2.0% and it was more common among females and in the obese (Ekerljung et al. 2011).

Asthma control

Asthma control reflects to the extent to which the various asthma manifestations can be reduced by treatment. The definition of asthma control is described in details 2.1.4. Although poor asthma control may be due to underlying severe disease or resistance to therapy, it is far more frequently due to poor compliance, poor inhaler technique, smoking or allergen exposure (Taylor et al. 2008a).

Only 10% of asthmatics were found to have asthma under control in the study of young adult population of Italy carried out between

1998 and 2000 (de Marco et al. 2003). At the beginning of 2000s in a worldwide survey including countries in North America, Europe and Asia current asthma control was also evaluated to be poor and the use of preventive medication to be low (Rabe et al. 2004). In another web-based survey 1812 patients were assessed, of whom 45% had controlled asthma and 55% uncontrolled asthma based on the score of the ACT (Peters et al. 2007). In this study all subjects had physician-diagnosed asthma for at least 1 year and were receiving multiple controller medications. In ECRHS II the distribution of asthma control was evaluated in a population-based setting with 1042 adult asthmatics. Overall 32% of asthmatics had completely controlled asthma, 36% partly controlled and 32% uncontrolled (Cazzoletti et al. 2007). This probably reflects the severity of the underlying disease which was more often uncontrolled among the subjects using ICS during last year: only 15% of them had controlled asthma, 49% had uncontrolled asthma and 36% partly controlled asthma. Uncontrolled asthma was also more common among ICS users in a French case-control and family study of asthma (Siroux et al. 2009). A total of 27.6% of ICS users had controlled, 35.0% partly-controlled and 37.4% uncontrolled asthma compared with non-ICS users having proportions of 60.0%, 23.9% and 16.1%, respectively.

Being a smoker, female and having a BMI greater than 30 kg/m^2 seem to be independent determinants of poor asthma control (Laforest et al. 2006) as well as long-term exposure to air pollution (Jacquemin et al. 2011). Additionally, a chronic cough and phlegm (Cazzoletti et al. 2007; Siroux et al. 2009), being female (Siroux et al. 2009), overweight (Cazzoletti et al. 2007) and having sensitisation to Cladosporium (Cazzoletti et al. 2007) have associated with poor asthma control in subjects using ICS. The reported risk factors of non-ICS users for poor asthma control have been partly different including high total IgE (Cazzoletti et al. 2007; Siroux et al. 2009), non-seasonal asthma (Cazzoletti et al. 2007), sensitisation to moulds (Siroux et al. 2009) and chronic cough and phlegm (Cazzoletti et al. 2007).

Occurrence of severe refractory asthma

Based on the WHO consultation severe asthma, includes three groups: (1) untreated severe asthma, (2) difficult-to-treat severe asthma, and (3)

treatment-resistant severe asthma (Bousquet et al. 2010). The last group includes asthma for which control is not achieved despite the highest level of recommended treatment and asthma for which control can be maintained only with the highest level of recommended treatment. This type of asthma is also called severe refractory asthma (Chanez et al. 2007). Bell et al suggested the step approach in which a person with uncontrolled asthma and/or at least two exacerbations during the past 12 months is firstly identified (Bel et al. 2011). Then it is confirmed that each of the following aspect is fulfilled: prescription of high dose ICS, confirmed asthma diagnosis, correct use of inhalers and asthma education received, good compliance with asthma treatment, excluding/controlling exposure to sensitising and non-sensitising substances at work and at home, discontinuing drugs that may cause bronchoconstriction, optimal treatment of co-morbidities, and reassessing the patient after at least 6 months follow-up. After these steps the diagnosis of severe refractory asthma can be established.

The prevalence of severe asthma is poorly known partly due to the variation in definitions. However, it is estimated that 5% to 10% of the population with asthma has symptomatic disease despite maximum recommended treatment with combinations of anti-inflammatory and bronchodilator drugs (Holgate et al. 2006). Typical characteristics of these subjects are the occurrence of frequent exacerbations, low baseline lung function, reliance on high dose corticosteroids and near daily symptoms. Subjects having severe refractory asthma represent a heterogeneous group of asthmatics, some of whom have a more severe form of allergic asthma, whereas many others do not. The risk factors identified for severe asthma are female gender, neutrophilic inflammation and being less atopic (ENFUMOSA 2003) as well as reporting less family history of allergy (Gaga et al. 2005).

Loss of lung function

Airway remodelling caused by chronic inflammation may lead to irreversible loss of lung function in asthma. This can be measured with spirometry by detecting persistent airflow limitation, usually defined by a low FEV_1, FEV_1/vital capacity or FEV_1/FVC of predicted after bronchodilatator administration, or increased loss of FEV_1. Persistent airflow

limitation is a sign of more severe disease and a predictor of mortality in the asthmatic population (Panizza et al. 2006).

Several investigations found that asthma is associated with increased decline in lung function (Peat et al. 1987; Ulrik et al. 1994; Phelan et al. 2002; Rasmussen et al. 2002; Sears et al. 2003). For example; Peat et al found that the average rate of decline in FEV_1 was 50ml/year in non-smoking asthmatics compared with 35ml/year in non-smoking non-asthmatic men (Peat et al. 1987). Data of the Childhood Asthma Management Programme suggested that about 25% of asthmatic children had a persistent decline in lung function that was not impacted by corticosteroid therapy (Covar et al. 2004). The irreversible loss of lung function seems to start already in childhood (Rasmussen et al. 2002).

Risk factors for progressive loss of lung function in patients with asthma include smoking (Ulrik 1999), adult onset (Ulrik 1999; ten Brinke et al. 2001), asthma severity (ten Brinke et al. 2001), BMI gain (Marcon et al. 2009), occurrence of severe asthma exacerbations (O'Byrne et al. 2009a) increased reversibility of obstruction (Ulrik 1999), increased numbers of airway eosinophils (Ulrik 1999; ten Brinke et al. 2001) and airway hyperresponsiveness (Ulrik 1999; ten Brinke et al. 2001).

As ICS are the first line therapy for persistent asthma, their effect on loss of lung function has been widely studied (Dijkstra et al. 2006; Lange et al. 2006; de Marco et al. 2007; O'Byrne et al. 2009b). The conclusions of these studies are that treatment with ICS may possibly decrease the rate of FEV_1 decline in asthma although there are no randomised double blinded studies that really prove such an effect.

2.3 Impact of work on asthma

2.3.1 Risk of asthma due to occupational factors

Evaluation of occupational risk of asthma

The literature in this field has methodological variability in several aspects. Firstly, the definition of asthma differs widely and can be based on reporting asthma symptoms or doctor diagnosed asthma in a questionnaire or on a clinically verified disease.

Secondly, the evaluation of occupational exposure varies. Large population samples are achieved with register studies, but the data on occupations is restricted to job titles and work tasks and exposures cannot be evaluated in detail (Karjalainen et al. 2001). Additionally, smoking data is often lacking and control of this important confounder is not satisfactory. In more specific (case-control or cohort) studies the work tasks and occupational exposure as well as smoking habits can be evaluated in detail, but participation rate varies and lack of power is a common problem due to a small number of subjects having worked in a certain occupation or having been exposed to a specific agent. Job Exposure Matrix (JEM) allows for the generation of more detailed exposure information from job title related information in large population based studies. During the last decade the use of JEM has gained increased support due to its relatively unbiased way to assess occupational exposure (Kennedy et al. 2000). The principals of JEM are described in a later section (2.5.2); briefly, JEM estimates the probable exposure to asthma inducing agents based on job titles and more detailed information on work tasks.

Thirdly, the type of population studied has effect on the associations between work and asthma. To illustrate some of the above methodological variability one can observe the asthma risk in painting or lacquering in different studies. In a large Finnish register based study, painting or lacquering work was associated with an approximate 2-fold risk with narrow confidence intervals (OR 1.92, 95%CI 1.70–2.17), but due to the job title based approach the authors could not evaluate the specific risk in spray painting (Karjalainen et al. 2001). The cross-sectional part of the ECRHS also showed an approximate 2-fold risk of clinically verified asthma among other painters (OR 2.34, 95%CI 1.04–5.28) and spray painters (OR 1.96, 95%CI 0.72–5.34), but both risk estimates had rather wide confidence intervals (Kogevinas et al. 1999). In the Spanish part of the ERCHS spray painters had an 8-fold risk of asthma, however without statistical significance (OR 8.01, 95%CI 0.65–99.02) (Kogevinas et al. 1996). A recent Swedish study showed a significantly increased asthma risk among male spray painters (OR 7.5, 95%CI 2.4–24.1) (Lillienberg et al. 2012). A higher risk among spray painters than other painters looks plausible when taking into account that spray painters are exposed to high levels of a respiratory sensitising chemical group, di-isocyanates, which are known to increase asthma risk (Lillienberg et al. 2012).

Calculating population attributable factor

The population attributable fraction (PAF) measures the fraction of disease cases that are attributable to exposure in a population and that would not have been observed if the exposure had been non-existent. The PAF quantifies the proportion of disease that can be attributed to a certain risk factor and is a critical measure of the adverse public health impact of that risk factor (Levin 1953; Northridge 1995; Nurminen et al. 2001; Steenland et al. 2006). The PAF can be calculated as follows:

$$PAF\% = Prevalence_{exp}(RR-1)/[1+ Prevalence_{exp} (RR-1)].$$

RR is the risk ratio or rate ratio (whichever measure was estimated) for the exposed Prevalence exp is the proportion of exposed in the population. As far as occupational factors are concerned, the fractions refer to the working aged population only, i.e. adult onset asthma.

Other terms like attributable risk/fraction or population attributable risk are sometimes also used, but in the chapters below PAF is used.

PAF due to workplace environment

In a review about 43 published citations from 1966 to 1999, the median value for the PAF of occupational exposure in asthma was 9% overall and 15% based on the 12 highest scored studies (Blanc et al. 1999b). A few years after this the American Society Statement carried out the critical synthesis of population-based literature on this field (Balmes et al. 2003). All published articles before January 2000 that include PAF calculations or presented data from which PAF could be calculated were analysed. The reported or calculated PAF range from 4% to 58% and had the median value of 15%. Accordingly to a recent systematic analysis including both earlier studies and articles from 1999 to December 2007 about 18% of adult-onset asthma is estimated to be caused by the workplace environment (Toren et al. 2009a).

In the prospective part of the ECRHS 6837 subjects without asthma were followed up for approximately 9 years. Asthma was assessed by methacholine challenge test and by questionnaire data on asthma symptoms or medication. The PAF for occupational exposures ranged

from 10–25% in cases of new-onset of asthma. The PAF was highest in southern Europe (23%) and lower in central (12%) and northern parts of Europe (6%) (Kogevinas et al. 2007). In the large Canadian general population study the PAF for adult-onset of asthma in high risk jobs and exposure was 18.2% (Johnson et al. 2000).

PAF in Nordic studies

In the RHINE study over 13 000 people from seven different areas in Denmark, Iceland, Norway, Estonia and Sweden were followed up from 1989–1992 to 1999–2001 (Lillienberg et al. 2012). Based on the questionnaire data, 429 new-onset cases of asthma occurred and asthma incidence was 1.3 cases per 1000 person-years for men and 2.4 for women. PAF for the proportion of new-onset of asthma due to exposure to agents at the workplace causing asthma was 14% for men and 7% for women.

The study basis of the Karjalainen et al study covered the entire population aged 25–59 year in Finland between 1986 and 1998. Their occupations were classified and the onset of asthma was followed-up. Altogether 49 575 incident cases of asthma were recognised from the Medication Reimbursement Register of National Health Insurance and Finnish Register of Occupational Disease (FROD). To obtain the reimbursement rights objective data on reversible bronchial obstruction and the typical symptoms of persistent asthma need to be demonstrated. The detailed criteria of these rights have varied during past decades, in 2001 at least one of the following physiological criteria were applied: 1) a diurnal variation of ≥ 20% in PEF, 2) an increase of ≥ 15% in PEF or FEV_1 with β_2-agonist, 3) a decrease of ≥ 15% in PEF or FEV_1 in exercise test. Additionally regular use of asthma medication had to last at least 6 months. The FROD is explained in detail in chapter 2.3.3). The PAF of occupation was as high as 29% for men and 17% for women (Karjalainen et al. 2001). However in this study the authors were not able to make adjustments with smoking status at an individual level, although occupation-specific aggregate data on smoking were used to estimate confounding by smoking.

Occupations with increased asthma risk

In the Spanish part of the ERCHS a study, population selected randomly from five different areas was evaluated firstly with questionnaire and later with clinical tests (Kogevinas et al. 1996). The participation rate in clinical tests was only 41% from the selected population. Cleaners (OR 2.53, 95%CI 1.03–6.20) and laboratory technicians (OR 9.29, 95%CI 3.28–26.2) had a significantly increased risk for clinically verified asthma. Welders, painters excluding spray painters, construction workers or miners and housewives showed a significantly increased asthma risk for asthma symptoms or use of asthma medication.

In the first part of the ECRHS the data of 15 637 people aged 20–44, randomly selected from the general population of 26 areas in 12 industrial countries was assessed in 1989–1992. Asthma was diagnosed by the metacholine challenge test and by questionnaire data on respiratory symptoms and use of asthma medication. Significantly increased asthma risk was shown in farmers (OR 2.62, 95%CI 1.29–5.35), painters (OR 2.34, 95%CI 1.04–5.28), cleaners (OR 1.97, 95%CI 1.33–2.92) and agricultural workers (OR 1.79, 95%CI 1.02–3.16). In the second part of the ECRHS, the highest occupational risks included nursing, cleaning, spray painting, baking and agriculture as well as exposure to high-molecular-weight agents, low-molecular-weight agents and irritants increased the asthma risk (Kogevinas et al. 2007).

A French study including over 14 000 adults found associations between asthma and specific jobs, such as personal care workers, waiters, and stock clerks were observed, with age-, sex-, and smoking-adjusted ORs between 1.5 and 1.7 (Le Moual et al. 2004). In a Canadian study nursing, clerical and food preparation associated most commonly with work-related asthma (Johnson et al. 2000). In the National Health Interview Survey 2001 over 20 000 currently employed adults in the population of the United States of America reported an association between working in printing/publishing industries and health care and asthma were found in whites. In blacks, significant associations were related to furniture/lumber/wood and entertainment/recreation industries (Bang et al. 2005).

Occupations with increased asthma risk in Nordic studies

In a Swedish nested case-referent study the asthma diagnosis based on reporting physician diagnosed asthma or asthma symptoms in a questionnaire (Toren et al. 1999b). The highest OR for physician diagnosed asthma was associated with exposure to flour dust (OR 2.8, 95%CI 1.5–5.2) and occupational handling of paints containing isocyanates (OR 3.0, 95%CI 1.6–5.9). Exposure to welding fumes, textile dust, and work with glues containing acrylates was also associated with an increased OR for "physician-diagnosed" asthma. In another case-control, study increased risks of asthma associated with exposure to welding fumes (OR 2.0, 95%CI 15–3.4), man-made mineral fibres (OR 2.6, 95%CI 1.4–7.3) and solvents (OR 2.2, 95%CI 1.2–3.2). In a large questionnaire study of a randomly selected population, over 18 000 subjects in west Sweden, occupational exposure to dust or fumes associated with new-onset of asthma (Hazard ratio, HR 1.8, 95%CI 1.4–2.3) (Toren et al. 2011).

In the Rhine Study occupations with highest risk of asthma among men were spray-painters (OR 7.5, 95%CI 2.4–24.1), plumbers/pipe fitters (OR 4.0, 95%CI 1.6–10.0), food and tobacco processing workers (OR 2.7, 95%CI 0.97–7.3), cleaners/building caretakers (OR 2.6, 95%CI 1.1–5.9) and child and other personal care work (OR 2.5, 95%CI 1.0–6.3) (Lillienberg et al. 2012). Among women cleaner/building caretakers (OR 1.9, 95%CI 1.2–3.0) and drivers (OR 3.7, 95%CI 1.2–11.6) had significantly increased asthma risk. Based on JEM, men exposed to plant-associated antigens, epoxy chemicals, di-isocyantes, cleaning agents and accidental peaks to irritants had significantly increased asthma risk. Additionally non-atopic men exposed to acrylates and women exposed to cleaning agents showed increased asthma risk.

In a large Finnish Register based study, Karjalainen et al reported increased asthma risks especially in occupations related to agriculture (RR 2.1, 95%CI 2.0–2.3 in men and RR 1.8, 95%CI 1.8–1.9 in women), mining (RR 2.0, 95%CI 1.6–2.4 in men, RR 1.0, 95%CI 0.3–4.0 in women), manufacturing (RR 1.6, 95%CI 1.5–1.7 in men and RR 1.3, 95%CI 1.3–1.4 in women), and service work (RR 1.5, 95%CI 1.4–1.7 in men and RR 1.4, 95%CI 1.4–1.5 in women) (Karjalainen et al. 2001). In the extended analyses of this same material Karjalainen et al used a more detailed level of occupational classification (three digit) (Karjalainen

et al. 2002). A significantly increased risk was found for either men or women in 125 occupations. For the men, the risk was highest among bakers, laundry workers, shoemakers and repairers, tanners, fellmongers and pelt dressers, and metal plating and coating workers. For the women, the risk was highest among shoemakers and repairers, railway and station personnel, jewellery engravers, engine room crew, moulders, round-timber workers and bakers. In a case-control study of 521 cases of new-onset of asthma from Tampere region, significantly increased asthma risk was reported among men in metal work (OR 4.52, 95%CI 2.35–8.70) and among female waitresses (OR 3.03, 95%CI 1.10–8.31) (Jaakkola et al. 2003).

Table 1 lists occupations that have frequently been associated with an increased asthma risk.

Table 1. Some occupations with increased risk of asthma

Occupation	References
Baking or other food processing or beverage work	(Kogevinas et al. 1996; Kogevinas et al. 1999; Johnson et al. 2000; Karjalainen et al. 2001; Jaakkola et al. 2003; Kogevinas et al. 2007; Lillienberg et al. 2012)
Agriculture, farming or forestry work	(Kogevinas et al. 1996; Kogevinas et al. 1999; Karjalainen et al. 2001; Kogevinas et al. 2007)
Cleaning/building caretaking	(Kogevinas et al. 1999; Karjalainen et al. 2001; Kogevinas et al. 2007; Lillienberg et al. 2012)
Spray painting or painting	(Kogevinas et al. 1996; Kogevinas et al. 1999; Karjalainen et al. 2001; Kogevinas et al. 2007; Lillienberg et al. 2012)
Nursing or other health care	(Johnson et al. 2000; Bang et al. 2005; Kogevinas et al. 2007)
Chemical processing	(Johnson et al. 2000; Karjalainen et al. 2001; Jaakkola et al. 2003)
Plastic working	(Kogevinas et al. 1999; Jaakkola et al. 2003)
Metal working	(Karjalainen et al. 2001; Jaakkola et al. 2003)
Woodwork	(Karjalainen et al. 2001; Bang et al. 2005)
Child and other personal care	(Le Moual et al. 2004; Lillienberg et al. 2012)
Waitressing	(Jaakkola et al. 2003; Le Moual et al. 2004)

The role of high-level exposure of irritants in the onset of asthma

Several epidemiological studies provide evidence on the impact of single or multiple high-level exposures to irritants in the initiation of asthma. In the Swedish study of sulphite workers asthma incidence was nearly 6-fold among males reporting sulphur dioxide gas exposure compared to unexposed males (Andersson et al. 2006). In another study bleacher workers exposed to ozone had an increased risk of physician diagnosed asthma and wheezing attacks (Henneberger et al. 2005). In the ECRHS II inhalation accidents, such as fire, mixing cleaning products, or chemical spills were associated with a 3.3-fold increased risk of new-onset asthma (Kogevinas et al. 2007).

2.3.2 Definitions of work related asthma, occupational asthma and work-aggravated asthma

In the previous chapter the work-related risk of asthma was assessed at population level. When looking at the same relation at individual level, important conceptual definitions need to be made. The evidence-based guidelines give the following definitions: "Asthma is work-related when there is an association between symptoms and work" (Nicholson et al. 2010). The different types of work-related asthma should be distinguished since the implications for the worker and the occupational health management of the disease differ. Work-related asthma includes two distinct categories:

1. "occupational asthma (OA), i.e. asthma induced by exposure in the work environment to airborne dust, vapours or fumes, in workers with or without pre-existing asthma"
2. "work-exacerbated asthma (WEA), i.e. pre-existing or coincidental new-onset adult asthma which is made worse by non-specific factors in the workplace e.g. cold, dry air, dust and fumes"

2.3.3 Occupational asthma

Occupational asthma can be subdivided into sensitiser-induced and irritant-induced OA. A latency period between first exposure to a respiratory sensitizer at work and the development of allergy symptoms is characteristic to sensitiser-induced OA. Irritant-induced OA occurs typically within few hours of a high concentration exposure to an irritant gas, fume or vapour at work (Tarlo et al. 2008; Nicholson et al. 2010). There is increasing epidemiological evidence for the relationship between multiple exposures to irritants and the onset of asthma and it has been postulated, that this type of asthma could be an occupational disease. However the diagnostic criteria on individual level are not established (Tarlo et al. 2008; Dykewicz 2009).

Over 400 agents have been identified to cause OA (www.asthme.csst.qc.ca) and many new agents are reported each year. Agents that cause allergic OA can be divided in two groups according to their molecular weight: high molecular (HMW) and low molecular weight agents (LMW) (Malo et al. 2009). The most typical HMW agents causing OA are cereals and flours, animal epithelium, latex and enzymes. Virtually all proteins of animal or plant origins are capable to cause IgE-mediated sensitisation, rhinoconjuctivitis and asthma. LMW agents causing OA include, e.g. anhydrides, di-isocyantes, metals, disinfecting agents, colophony used as a flux in electronic industry. The commonest agents causing irritant induced OA are chlorine and ammonium, but many other agents have also been implicated (Tarlo et al. 2008).

Based on the recent evidence-based report atopy is considered to increase risk of developing OA caused by exposure to many HMW-agents (Nicholson et al. 2010). Cigarette smoking can increase the risk of OA with some sensitising agents, while occupational rhinitis is considered to be a co-morbidity factor with OA. In a study of Karjalainen occupational rhinitis increased the risk of asthma nearly 5-fold (Karjalainen et al. 2003).

Clinical, functional and pathophysiological alterations are considered to be similar in OA and non-OA (Bernstein et al. 2006). HMW and some LMW agents typically induce Th2 cytokine/ IgE mediated inflammation, while some other chemicals (isocyanates, methacrylates) are considered to induce asthma through immunological mechanisms

that may be independent of classical IgE-mediated pathway. In a study of Anees et al of 38 workers with OA caused by LMW agents only 37% had sputum eosinophilia (Anees et al. 2002). The mechanisms of irritant induced asthma are poorly understood. It has been speculated that the inhalation of high-level irritant may cause bronchial epitehelium damage which could induce the loss of its protective function (Lemiere et al. 1997).

Diagnosis and management

Partly due to different legislation for compensation of occupational diseases, the diagnostic practices vary worldwide. In sensitiser induced OA commonly used diagnostic tests include proving sensitisation, peak flow recording at work and at home, changes in hyperreactivity and specific inhalation challenge test (SIC) (Tarlo et al. 2008; Nicholson et al. 2010; Lindstrom et al. 2011; Suojalehto et al. 2011). The last mentioned test is considered to be a golden standard for diagnosing OA to a specific sensitiser. SIC is an expensive and time consuming test and false negatives as well as severe asthmatics or anaphylactic reactions are possible (Vandenplas et al. 2012). Therefore, the use of SIC is restricted to a few centres (approximately 30 centres in Europe, personal information by Hille Suojalehto) and in many countries the diagnosis of OA is based on the other diagnostic tests mentioned above and/or typical pattern of disease.

In Finland OA entitles workers to a relatively generous compensation including the re-training costs, when it is required. Therefore a reliable diagnosis OA is needed and SIC is commonly used. However, in the recent recommendation of the Finnish Expert Group on Occupational Lung Diseases it was concluded that OA can be diagnosed without SIC, when there is a typical pattern of disease, asthma has been proven, clear sensitisation to a relevant occupational agent is shown and PEF recording at work and at home is typical for OA (Suojalehto et al. 2011).

Based on the recent European Respiratory Society Task Force Report the best treatment option for OA is ceasing exposure to the causative agent (Baur et al. 2012). If it is not possible, reduction of exposure is the second best option, whereas respirators are of limited value.

Incidence and causes

There are differences between the reporting schemes for occupational diseases and National Registers are lacking in many countries (Bakerly et al. 2008). Additionally heterogeneity in definition, diagnostic approaches, legislation, and compensation of OA exists. Therefore the comparison of incidence of OA in different countries is a challenge. There are only few studies showing the incidence rates at population level.

In Catalonia, both compulsory and voluntary reporting systems have been used and the latter proved to be more efficient (Orriols et al. 2006). Based on the voluntary reporting scheme the annual rate of OA was 77.2 cases/million persons in 2002 and the most frequent causes were isocyanates, persulphates and cleaning products. In the West Midlands, UK, a voluntary reporting scheme by physicians has been used and the annual incidence of OA was 42 per million working population in 1991–2005 (Bakerly et al. 2008). Welders and occupations related to health care were the two most frequently reported occupations with OA, while isocyanates were the most common causative agents.

In Sweden registration has been based on employees' own reports and the overall annual rate of OA was 91/million for men and 70/million for women in 1990–1992 (Toren 1996). The highest rates among men were working as bakers, furnace men and welders and among female chemical and plastic production workers and poultry and dairy farm workers.

Finnish Register of Occupational Disease

Reporting all known or suspected cases of occupational diseases to labour protective authorities is compulsory for Finnish physicians. These reports and complementary data from insurance companies are collected in the FROD. Due to changes in communication arrangements and principles regarding compensation, the data for 2005 onward is comparable, but it should not compared directly with earlier FROD data. Since 2005 the numbers of suspected cases and those verified by an insurance company have been presented separately.

Using the FROD data, Karjalainen et al reported 2602 incident cases of OA between 1989 and 1995 and an annual incidence rate of 174/million employed workers (Karjalainen et al. 2000). The incidence

rate was the highest in bakers, other painters and lacquerers, veterinary surgeons, chemical workers, farmers, animal husbandry workers, other food manufacturing workers, welders, plastic product workers, butchers and sausage makers, and floor layers. Cases caused by animal epithelia, hairs and secretions or flours, grains, and fodders accounted for 60% of the total. Piipari et al reported the decreased trend of OA cases starting between 1995–1998 and indoor molds becoming the most common causative agent in 2002 (Piipari et al. 2005).

The numbers suspected and verified OA cases and their proportions of estimated new asthma cases of the total working population in 2005–2010 are presented in table 2. The estimation of incident asthma cases is based on the annual incidence rate of the general population study of Helsinki area, (Pallasaho et al. 2011), while the total workforce is nationwide and non-employed individuals are not included. Therefore the data should be interpreted with caution. Nevertheless, 5–8% of the new asthma cases of the working population seem to have suspicion of OA and only 1–2% of the cases are verified to OA by worker's compensation scheme. As approximately 18% of adult-onset asthma is estimated to be caused by occupational exposures (Toren et al. 2009a), one might conclude that only about one in ten of those cases is getting individual level confirmation and compensation for occupational disease based on the Finnish practices. In the recent reports of the FROD the highest OA figures were notified in the food industry and agricultural occupations (Oksa et al. 2009; Oksa et al. 2010). The most common causes of OA were indoor moulds, flour, grain and animal feed as well as animal epithelia, hair and extracts. The most common chemicals causing asthma were cosmetics substances, resins, plastics and di-isocyanates.

Table 2. Number of suspected and verified occupational asthma cases in 2005–2010 and their proportions of estimated new asthma cases of the total working population based on the data of Finnish Register of Occupational Disease

Year	Total working population (n)	Estimated incident asthma cases (n)*	Suspected OA cases (n)	Suspected OA cases %**	Verified OA cases (n)	Verified OA cases %**
2005	2400811	8883	499	5.6	143	1.6
2006	2443477	9041	523	5.8	145	1.6
2007	2491638	9219	551	6.0	116	1.3
2008	2530898	9364	612	6.5	120	1.3
2009	2457265	9092	679	7.5	152	1.7
2010	2447482	9056	708	7.8	102	1.1

* = The estimation is based on the annual incidence rate of 3.7/1000 persons (Pallasaho et al. 2011) and the number of total working population
** = of the number of estimated incident asthma cases in total working population

2.3.4 Work-exacerbated asthma

WEA is defined as "pre-existing or concurrent asthma that is worsened by workplace conditions" (Henneberger et al. 2011). Based on the recent ATS Statement, the following four criteria can be used in both clinical and research settings to identify the subjects with WEA:

1. Presence of pre-existing or concurrent asthma
2. Temporal relationship between exacerbation of asthma and work
3. Conditions exists at work that can exacerbate asthma
4. OA is unlikely

Prevalence

In most population-based studies of WEA both asthma diagnosis and the presence of WEA are based on self-reports. Some of the studies report a prevalence of WEA as a percentage of working adults with asthma (Mancuso et al. 2003; Saarinen et al. 2003; Bolen et al. 2007) and some as a percentage of all adults with asthma (Blanc et al. 1999a;

Henneberger et al. 2002). In some of the studies both of these parameters were presented (Henneberger et al. 2003; Henneberger et al. 2006). In the twelve general population-based studies referred in the ATS statement the prevalence of WEA ranged from 13% to 58% with a median 21.5% (Henneberger et al. 2011).

In the study of over 1400 asthma cases enrolled in Health Maintenance Organization of United States, 25% of the responders reported their current work environment as having a worsening effect on their asthma (Henneberger et al. 2002). In a population-based questionnaire study by the State of Maine only 64 asthma cases were identified and 25% of these subjects reported worsening of asthma symptoms at work (Henneberger et al. 2003). In a third study by Henneberger et al 557 working participants with asthma based on the medical record data were identified from a register held by the Health Maintenance Organization (Henneberger et al. 2006). The occurrence of WEA was based on self-reports of work aggravated symptoms and expert judgment that a participant was likely exposed to asthmogenic agents at work. A total of 23% of all asthmatics and 24% of working asthmatics fulfilled the criteria of WEA.

In a Brazilian birth cohort study of young adults, the ECRHS questionnaire was used and 227 cases of clinically verified asthma were identified (Caldeira et al. 2006). Based on the personal interview 81(32%) cases of work-related asthma were found. Johnson et al. reported an 18% prevalence of WEA in currently employed adult asthmatics in the Australian general population (Johnson et al. 2006).

Nordic studies

Blanc reported in the Swedish part of the ECRHS that 61 (38%) subjects from 160 participants with clinically verified asthma reported chest tightness at work (Blanc et al. 1999a).

In the Finnish population-based survey the asthma cases were identified from the Medication Reimbursement Register of National Health Insurance and work related asthma symptoms were evaluated with the questionnaire (Saarinen et al. 2003). A total of 21% of the currently employed 969 respondents reported work-aggravated asthma symptoms at least weekly during the past month.

Causes

Those with WEA have been reported to be less educated (Henneberger et al. 2002; Caldeira et al. 2006). One study reported an increased risk in current or ex-smokers and males (Henneberger et al. 2002), while these associations were not present in the large Finnish study (Saarinen et al. 2003), in which the prevalence of those with WEA increased by age. WEA has also been associated with self-reported more severe asthma (Henneberger et al. 2002) and recent asthma symptoms (Henneberger et al. 2006).

The proportion of WEA of all asthma cases has been reported to be highest in service work (Goe et al. 2004), mining and construction (Henneberger et al. 2002), sales work (Henneberger et al. 2002; Goe et al. 2004), and administration (Henneberger et al. 2002; Goe et al. 2004).

WEA is often associated with irritant exposures (Tarlo et al. 1995; Saarinen et al. 2003; Goe et al. 2004) and second-hand tobacco smoke (Tarlo et al. 1995; Berger et al. 2006). In the Saarinen study, the prevalence of those with work-aggravated symptoms increased by self-reported occupational exposure to dust, abnormal temperatures or poor indoor air quality, physically strenuous work and expert-evaluated probability of daily occupational exposure to airborne dust, gases or fumes (Saarinen et al. 2003). Lemiere et al compared occupational exposure in OA and WEA in the patients of tertiary care clinic and demonstrated that those 53 patients with WEA were exposed to ammonia, engine exhaust fumes, silica, mineral fibres, aerosol propellants and solvents significantly more often than the 68 OA cases (Lemiere et al. 2012).

Clinical characteristics

There are only a few studies available. PEF recording at work and at home showed a typical pattern in only about half of the WEA cases (Chiry et al. 2007). The risk of asthma exacerbations was increased when compared to subjects with non-work related asthma both in WEA and in OA (Lemiere et al. 2007). Vandeplas et al reported that 61% of 105 WEA patients from a tertiary care hospital had nasal symptoms (Vandenplas et al. 2010). In a prospective observational survey with a 2-year follow-up 53 WEA, 68 OA and 33 subjects with non-work related asthma were evaluated

(Lemiere et al. 2013). The authors collected baseline data on the visit to the tertiary medical clinic and follow-up data based on the provincial administrative databases. WEA was associated with more frequent prescriptions of inhaled corticosteroids, a noneosinophilic phenotype, a trend toward a lower FEV_1 and a higher proportion of smokers than the diagnosis of OA. Both OA and WEA were associated with greater health care use and 10-fold higher costs related to outpatient clinical visits, emergency department visits and hospitalisations than non-work related asthma.

2.3.5 Severity and occurrence of exacerbations

There is conflicting data on the influence of occupational exposure on asthma severity. Gaga et al. found that a larger proportion of severe asthma patients reported symptoms at work or changes of jobs, while exposure at work to gas, dust or fumes did not differ compared with the group of subjects with mild asthma (Gaga et al. 2005). LeMoual et al studied 228 controls without asthma and 148 asthmatics including 78 severe and 70 mild asthma cases (Le Moual et al. 2005). JEM based exposure to HMW-agents (OR 3.7, 95%CI 1.3–11.1), LMW-agents (OR 4.4, 95%CI 1.9–10.1), including industrial cleaning agents (OR 7.2, 95%CI 1.3–39.9) and mixed environmental agents (OR 7.5, 95%CI 2.4–23.5) was significantly associated with more severe adult-onset asthma, although confidence intervals were broad due to a small number of asthmatics. In childhood-onset asthma, exposure to asthmogens was not associated with asthma severity.

In the prospective part of the ECRHS with 966 working adults with asthma, Hennenberger et al defined asthma exacerbation as unplanned care for asthma in the past 12 months (Henneberger et al. 2010). High dust, gas and fumes exposure was associated of a 3-fold risk of exacerbations (RR 3.1, 95%CI 1.9–5.1). Based on this RR, the population attributable risk was 14.7% among workers with current asthma and a total of one in seven asthma exacerbations was estimated to be of occupational origin.

In a Swedish general population based study of approximately 1700 participants with asthma, 24% of the asthmatics had multi-symptom asthma (Ekerljung et al. 2011). Work-related exposure to gas, dust and

fumes was linked to multi-symptom asthma, which was considered to be a sign of more severe asthma.

2.3.6 Healthy worker effect

"The healthy worker effect (HWE) is the potential bias caused by the phenomenon that sicker individuals may choose work environments in which exposures are low; they may be excluded from recruitment, or once hired; they may seek transfer to less exposed jobs or leave work" (Li et al. 1999). This bias has been well described in occupational mortality studies

The HWE leads to the less healthy worker leaving work during follow-up. HWE has proved to be a more important bias for diseases appearing at young age, presenting early symptoms and having a short period of latency between exposure and symptoms (Chen et al. 1996). Therefore asthma is potentially a disease, in which HWE plays an important role. Le Moual stated that "Controlling of this bias needs prospective studies including dynamic cohorts, which can enter the study population, when they are hired and are followed even after they leave employment" (Le Moual et al. 2008). The time-varying exposure and its relation to asthma related factors need to be well documented.

In a follow-up study of Israeli military conscripts, job changes were seen among the asthmatics more frequently than among the controls, especially among those with a more severe form of the disease (Kivity et al. 1995). In the ECRHS study, the respondents with asthma manifesting before completion of full-time education were at a decreased risk of having jobs with high risk of asthma or exposure to dust, gases or fumes (Olivieri et al. 2010). It was concluded that having asthma prior to entering the workforce may affect a person's career path. Whether this choice was done prior or after full-time education could not be determined. In contrast, a French follow-up study of asthma cohort suggested a healthy worker hire effect in subjects with more severe or symptomatic asthma in childhood, because these subjects were less likely to be exposed to the asthmogens in their first job (Dumas et al. 2011).

2.4 Work ability

2.4.1 Conceptual framework and definition

The diversity of work ability makes its evaluation and definition a challenge (Gould et al. 2008). One basic question in evaluating work ability is the perspective from which it is evaluated. The evaluation of work ability can be thus based on the person's own view or it can be made by health care or social insurance professionals. Determining work ability solely according to objective criteria or expert evaluation is problematic, due to the complex nature of the concept. In fact, subjective estimations have proved to be a good predictor of future work ability or disability (Ilmarinen et al. 1997). Cessation of employment and disability pension are the most severe consequences of reduced work ability. Temporary sick leave, change of employer, job or work tasks and reduced self-assessed work ability are more common and have an impact on work productivity. Furthermore a high rate of sickness absenteeism has been shown to increase the risk of job termination and unemployment among women in temporary public sector jobs (Virtanen et al. 2006).

Health and work are the main determinants of work ability. Work related factors, such as work tasks, work conditions, occupational roles and an organisation's values can influence a person's work ability. Worker's physical and mental capacity, occupational skills and general skills are also important factors. The variation of work ability by age is wide and younger people perceive their work ability to be much better than older people, while men and women have no significant differences in their self-estimated work ability (Gould et al 2008). In the Finnish Health 2000 survey clear difference in perceived work ability were found between five different educational groups (higher academic, higher vocational, secondary, upper basic and basic education) and the level of work ability increased as the level of education increased.

2.4.2 Asthma and work ability

Based on the current knowledge asthma is associated with decreased work ability, although the outcomes as well as populations studied are highly variable. Only few longitudinal studies on the effect of asthma on work

ability exist (Blanc et al. 1993; Thaon et al. 2008; Kauppi et al. 2010; Hakola et al. 2011), especially those based on the general population (Toren et al. 2009b). Table 3 summarises some studies about asthma and work ability.

Labour force participation, disability pension

In a population survey of adults in Northern California aged 18–50 year those with asthma were more likely to have no labour force participation after diagnosis (OR 3.0, 95%CI 1.1–7.7) and less likely to report decreased job effectiveness among those remaining employed (OR 0.4, 95%CI 0.2–0.9) compared with the rhinitis group (Blanc et al. 2001). Yelin et al reported in another U.S. population based study an elevated risk of leaving work prior to age 65 among persons with COPD, asthma or rhinitis (Yelin et al. 2006). Thanon et al. followed-up from 1990 to 1995 over 10 000 of working aged participants including 398 subjects with asthma (Thaon et al. 2008). In 1995, current adult-onset asthmatics had stopped working due to disability more frequently than never-asthmatics. In a study of 465 subjects with severe asthma 14% reported having left the workforce due to asthma and among those being currently employed 38% reported partial asthma-related work disability (Eisner et al. 2006).

Based on the study of the Finnish National Asthma Programme in 1993, 7212 patients of working age (9% of 80 133 asthmatics) received a disability pension from the Social Insurance Institution compared with 1741 in 2003 (1.5% of 116 067 asthmatics) (Haahtela et al. 2006). In a study of 2332 asthmatic and 66 354 non-asthmatic public sector employees in Finland asthma increased the risk of all long-term work disability causes with HR 1.8 (95%CI 1.62–2.09) compared to controls without asthma (Hakola et al. 2011). Asthma accompanied with another chronic disease increased the risk 2.2-fold (95%CI 1.8–2.8) and with two or more other chronic conditions 4.5-fold (95%CI 3.0–6.8). Asthma and depression increased the risk with HR 3.6 (95%CI 2.6–5.0), and the risk was especially high for permanent work disability (HR 6.8, 95%CI 4.6–10.2).

Change of job due to respiratory symptoms

Change of job due to work-related respiratory symptoms was reported to be common among persons with asthma in two asthma outpatient clinic studies (Blanc et al. 1993; Blanc et al. 1996), in two cross-sectional general-population studies (Blanc et al. 1999a; Blanc et al. 2003) and in a prospective study (Toren et al. 2009b).

In the Swedish part of the ECRHS, 4% of the total study population and 13% of those 350 participants with asthma reported a job change or work loss due to breathing affected by a job (Blanc et al. 1999a). In the cross-sectional part of ERCHS, 4% of the total population and 11% of the participants with asthma or chronic bronchitis reported a job change due to breathing difficulties at work (Blanc et al. 2003). Occupations with a high risk of asthma and self-reported job exposure to vapours, gases, dust, or fumes (VGDF) were associated with reduced work ability in both these studies, while self-reported exposure to environmental tobacco smoke at work showed an association only in the Swedish part of the ECRHS study.

In the prospective part of the ECRHS, data from 11 European countries and 1 centre in the U.S was evaluated (Toren et al. 2009b). There were 6659 randomly sampled controls and 779 subjects reporting physician-diagnosed asthma at baseline and the mean follow-up time was 9 years. The incidence rate of job change due to breathing problems was 1.2/1000 person-years of observation in the random sample (95%CI 1.0–1.5) and 5.7/1000 person-years in the asthma cohort (95%CI 4.1–7.8). In the asthma cohort, female sex (HR 2.8, 95%CI 1.3–5.9) and high occupational exposure to biological dust, mineral dust or gases or fumes predicted increased risk of job changes.

Murgia et al. demonstrated that a change of job or work task due to respiratory problems was common among pulp mill workers (Murgia et al. 2011). Asthma increased the risk of respiratory work disability 6.7-fold (95%CI 4.1–11.0). Interestingly a clear association between irritant peak exposures and work disability was found both in workers with asthma and workers without any chronic respiratory disease.

Work absenteeism

Nathel et al used both register and questionnaire based information on reasons for sick-leave and demonstrated that asthma is an underdiagnosed disorder in sick leave registers (Nathel et al. 2000). In another study obesity was found to be more frequent among asthmatics on sick leave, when compared with the non-specific pain patients on sick leave and the controls (Nathell et al. 2002).

In a Danish study, the register data for receiving unemployment, welfare, sick-leave and disability benefits over a 5-year period was combined with the ECRHS II screening questionnaire data in 7241 persons (Hansen et al. 2012). Adult-onset asthma was significantly associated with receiving disability (Prevalence rate ratio, PRR 2.4, 95%CI 1.7–3.4), sick leave (PRR 1.3, 95%CI 1.1–1.6) and welfare benefits (PRR 2.0 95%CI 1.6–2.0), while childhood-onset disease only had marginal correlations. Blue collar work significantly increased the probability of all public transfer incomes.

Kauppi et al. reported in a prospective cohort study of 48 296 Finnish public sector employees, that mean sick leave days per year for respondents were 17.6 days for rhinitis alone, 23.8 days for asthma alone and 24.2 days for both conditions combined (Kauppi et al. 2010). Respondents with neither condition were absent for a mean of 14.5 days annually. Rhinitis, asthma and both these conditions combined increased the risk of days off work, but the impact of asthma and rhinitis combined on the risk of sick leave days was marginal compared to asthma alone (RR 1.1, 95%CI 1.0–1.3).

Self-estimated work ability

In a Swedish study of 332 subjects with recent-onset asthma, 56% estimated having full (100%) work ability (Balder et al. 1998). Significant predictors for decreased work ability (< 100%) were asthma severity, workplace-associated respiratory symptoms and bronchial hyperresponsiveness. However there were no controls in this study.

Table 3. Some studies of asthma and work ability

Reference	Setting	Population	Asth-matics	Controls	Outcome	Result	Risk factors
Blanc et al. 2001	Cross-sectional	North-Carolina 18–50 years of age	125	175 with rhinitis	No labour force participation after diagnosis	Elevated risk OR 3.0 (1.1–7.7)	
Yelin et al. 2006	Cross-sectional	U.S population 55–75 years of age	115	597	Leaving work prior to 65 years	Elevated risk	
Thaon et al. 2008	Prospective	French men 37–52 years of age	398	10 205	Disability	Elevated risk in a subgroup** OR 3.8 (1.5–9.8)	
Eisner et al. 2006	Prospective	North California Hospitalization due to asthma < 65 years	465	–	Leaving workforce Partial work disability	Leaving workforce 14% Partial work disability 38%	Ex-smoker Less educated Severe asthma
Hakola et al. 2011	Prospective Register	Public sector workers	2332	66 354	Long-term work disability	Elevated risk HR 1.8 (1.62–2.09)	Co-morbidities Depression
Blanc et al. 1993	Prospective	Outpatient clinic	42	–	Change duties/ job/payment*	5-year cumulative index 36%	Asthma severity
Blanc et al. 1996	Cross-sectional	Outpatient clinic	601	–	Work cessation Change duties*	Work cessation 7% Change duties* 10%	Asthma severity
Blanc et al. 1999a	Cross sectional	Swedish ECRHS 20–44 years of age	350	1715	Job change/ work loss *	13% , (vs. 2% in controls)	High asthma risk occupation ETS VGDF exposure

Blanc et al. 2003	Cross-sectional	ECRHS 20–44 years of age	2528 with respiratory symptoms	15 039	Job change *	11% in subjects with asthma/COPD (vs. 2% in subjects without asthma)	VGDF exposure Ex-smoker
Toren et al. 2009b	Prospective	ECRHS 20–44 years of age	779	6659 Random sample	Job change *	5.7/1000 person-years in asthmatics 1.2/1000 person-years in controls	Female sex High occupational exposure ***
Murgia et al. 2011	Cross-sectional	Pulp mill workers	235	2985 Without asthma	Job/work task change*	Elevated risk HR 6.7 (4.1–11.0)	Irritant peak exposure
Kauppi et al. 2010	Prospective	Employed public sector workers	3159	33 442	Sick-leave days/year	Elevated risk OR 1.5 (1.3–1.6) for asthma OR 1.7 (1.6–1.8) for asthma+rhintis	
Mancuso et al. 2003	Cross-sectional	Outpatient clinic	196	-	Job/duty change Sick-leave due to asthma	Job/duty change 38% Sick-leave due to asthma 65%	Less educated Co-morbidities Asthma medication
Balder et al. 1998	Cross-sectional	West-Sweden New-onset asthma	332	-	Self-estimated	44% had decreased (< 100%)	Asthma severity Work-related symptoms Hyperreactivity
Hansen et al. 2012	5-year register based follow-up	Danish ECRHS II	664	6479	Disability Sick leave Welfare Unemployment	Elevated risk in adult-onset asthma of Disability, PRR 2.4 (1.7–3.4) Sick leave, PRR 1.3 (1.1–1.6) Welfare, PRR 2.0 (1.6–2.4)	Adult-onset asthma Blue-collar worker

* = due to breathing problems
** = in those 95 subjects with current adult-onset asthma
*** = to biological/mineral dusts, gases or fumes

ETS = environmental tobacco smoke
VGDF = self-reported occupational exposure to vapours, gases, dust, fumes
ECRHS = European Community Respiratory Health Survey
OR = odds ratio
PRR = prevalence rate ratio

2.5 Assessment of occupational exposure in epidemiological studies

2.5.1 Self-reported, job title, expert judgement

In earlier large population-based studies occupational exposure estimation was based on self-reports or job titles. However both these approaches have limitations. The potential limitation of self-reports is that asthmatic workers may be more likely to report certain exposures, especially if this exposure aggravates asthma symptoms (de Vocht et al. 2005). This phenomenon is called reporting bias.

The job or industry titles are less likely to be affected by reporting bias, but they are relatively poor surrogates for exposure to specific occupational agent. Professional judgement of occupational hygiene experts based on job titles and tasks has proved to be a good method of assessing occupational exposure. However, it is time-consuming and expensive and also dependent on the skills of the expert.

2.5.2 Job exposure matrix

Due to the limitation of the methods mentioned above a new approach, in which the job titles are merged with an external JEM was developed in the 1980s. The first JEM were generated and used for population-based cancer studies (Pannett et al. 1985). In the first part of the ECRHS a matrix that classified respiratory exposure into three broad general categories, mineral dust, biological dust and gases or fumes was used (Kogevinas et al. 1999). Each occupation type was classified as non-exposed, exposed to low levels and exposed to high levels of each of the three groups of pollutants.

Kennedy et al developed the asthma specific JEM in 2000 in order to assess exposures relevant to OA (Kennedy et al. 2000). The matrix is two dimensional with job codes on one axis and exposure categories on the other. The job codes are from the international classification of occupations (ISCO). The exposure axis contains 22 exposure groups including 18 high risk groups based on known risk factors for OA, divided into high molecular weight agents, low molecular weight agents, and mixed environments. In practice an experienced coder needs to revise codes before

applying the JEM. The matrix also flags "needs individual re-evaluation", when the exposure estimation is not reliable without description of work tasks. Table 4 demonstrates the use of asthma specific JEM. The asthma specific JEM by Kennedy has been used in several studies (Saarinen et al. 2003; Le Moual et al. 2004; Le Moual et al. 2005; Dumas et al. 2011), although JEM based exposure assessment has been argued to be a potential cause of misclassification (Lillienberg et al. 2012).

Table 4. An example of the use of asthma specific job exposure matrix by Kennedy

Job title	ISCO-88 code	Matrix exposure group	Possible change required
Baker	7412	HMW, flour	No
Life science technicians	3211	HMW, derived from animals	Class as exposed if job title or description of work tasks suggests laboratory animal exposure

ISCO = International classification of occupations
HMW = high molecular weight agent

Recently a Swedish group has developed a new asthma-JEM for the countries in northern Europe named N-JEM (Lillienberg et al. 2012). The same principles as in earlier respiratory specific JEMs (Kogevinas et al. 1999; Kennedy et al. 2000) is used in this new N-JEM, but the working conditions in northern Europe are taken into account. N-JEM includes six main groups: HMW agents, LLMW agents, irritating agents, 'accidental peak exposure to irritants', 'uncertain or low exposed group' and an unexposed reference group.

2.5.3 Some comparisons between the methods used

In the ECRHS I, the specificity of self-reported occupational exposure to VGDF was relatively high among asthmatics, approximately 0.83, but the sensitivity was relatively low (0.48), when compared with the JEM evaluation (de Vocht et al. 2005). In non-asthmatics the corresponding specificity and sensitivity were 0.87 and 0.42. Self-reported exposure,

but not JEM based exposure was more prevalent in the areas where asthma was more common. It was concluded that reporting occupational exposure seems to be dependent on asthmatic health status both at individual and at community level. Therefore self-reported exposure might be biased and should be used only in combination with more objective data on occupational exposure.

Quinlan et al. reported the sensitivity and specificity of VGDF against JEM to be 71% and 66%, respectively (Quinlan et al. 2009). Interestingly, 32% of those 199 subjects with the same job in two distinct interviews had discordance in self-reported exposure to VGDF. In a study of 176 hospital workers, Donnay et al. found large underestimation of self-reported exposure regarding to cleaning and disinfecting agents and a lack of knowledge of product components (Donnay et al. 2011).

3 AIMS OF THE STUDY

The aim was to study the short-term and long-term asthma prognosis and the effect of asthma on work ability in men with asthma since youth.

The more specific objectives were:

1. To evaluate the determinants of asthma severity among young male asthmatics (a) over a period of 6 to 12 months of military service during which they were exposed to many predisposing factors for asthma and (b) conduct a further evaluation of these effects at a follow-up two years later. (Study I)
2. The impact of individual characteristics and lung function tests at the age of around 20 as a risk factor for persistent asthma at the age around 40 (Study II)
3. The work ability at around 40 years of age and risk factors for decreased work ability in men with asthma since youth (Study III)
4. The effect of current work and workplace exposures on current asthma severity, asthma control and occurrence of exacerbations at around 40 years of age in men with asthma since youth (Study IV)

4 MATERIAL AND METHODS

4.1 Subjects and design

We used Finnish Defence Force registers to select the study population. In Finland it is obligatory for all young men of sufficiently good health to participate in either military or civil service. Up to 98% of all men underwent a medical examination at the age of 18–19. Subjects having mild asthma with normal lung function were evaluated as fit for most service duties. Those having stable moderate asthma and good lung function were evaluated as fit for restricted duties. Subjects with unstable or deteriorating asthma, or clearly decreased lung function, were exempted from military service. In the 1980s, about 90% of young men carried out 8–11 months military service and in the 2000s about 81% of young men participated in 6–12 months service.

According to Finnish Defence Forces' statistics, asthma is a common diagnosis among young men in military service and the major somatic reason for discharge from service. Many factors can aggravate asthma symptoms during military service, such as recurrent respiratory infections, physical exercise, and exposure to cold air, allergens or other dusts. Conscripts from all parts other than the northernmost regions of Finland with suspected or aggravated asthma are examined in the Central Military Hospital. Two types of asthmatics are identified from the register of the Central Military Hospital. Men with earlier diagnosed asthma were admitted to hospital due to unstable or aggravated asthma and were mainly admitted for the purpose of restarting or adding medication or for evaluation of service ability. The other group had a new-onset asthma and came for confirmation of the diagnosis.

4.1.1 Study I

All 216 men with verified asthma in 2004–2005 from the register of the Central Military Hospital were included in the study base. These subjects represented an unselected population of men with mild or moderate asthma aged 18–27, from southern and central parts of Finland. A follow-up questionnaire was sent approximately two years later in autumn 2007. The mean follow-up time (time between completing military service and completing the questionnaire) was 29 months. Of the 216 men, 69 did not respond to the questionnaire after two reminders and one did not give his consent for the study and were therefore excluded. The response rate of the questionnaire was 68% and the final study population comprised 146 subjects. The diagnosis of asthma was based on medical records.

In this study we evaluated asthma severity during military service according to medical records and two years after service according to the questionnaire and studied the value of lung function tests and allergy tests during military service as prognostic factors for current asthma severity.

4.1.2 Studies III and IV

Asthma Group 1 (n = 505) consisted of all subjects who were referred to the Central Military Hospital between 1987–1990 due to a diagnosis of asthma (including both men in military service with asthma already diagnosed before the service, and men with a new-onset asthma during service). This group represented an unselected population of men, who had mild or moderate asthma and were living in southern and central parts of Finland at the age of 18–27.

Asthma Group 2 (n = 393) included men who were exempted from military service in 1986–89 due to asthma and were alive in January 2009, representing an unselected population of Finnish men with relatively severe asthma at the age of 18.

The controls (n = 1500) were randomly selected from the 7,433 young men who entered military service in five large military units in Southern Finland between 1986 and 1990, who had no asthma diagnosis during military service according to the Defence Force register and were alive in January 2009. The 28 subjects reporting in the study questionnaire

as having asthma during their military service were excluded. The controls represented an unselected population of men, without asthma or any other disabling illness in their youth and who lived in southern or central parts of Finland. The description of the study is presented in more detail in figure 1.

A postal questionnaire was sent out in the spring of 2009, that is approximately twenty years (18–23 years) after military service or exemption at call-up. After two reminders, 232 men (54%) from Asthma Group 1, 161 men (44%) from Asthma Group 2, and 608 (44%) of the controls answered and thus comprised the final study population for the studies III and IV.

In study III, work ability was an outcome variable and among others current asthma severity and work exposure were explanatory variables. In study IV, current asthma severity, control and occurrence of exacerbations were end points, which were explained by current work exposure, professional status and release of asthma symptoms on days off.

4.1.3 Study II

All 232 respondents of the follow-up questionnaire from Asthma Group 1 were invited to clinical tests at the Finnish Institute of Occupational Health (FIOH). A total of 119 (51.3%) respondents accepted and attended the tests between August 2009 and April 2010, i.e. approximately twenty years (18–23 years, mean 21.1 years) after their military service and these respondents comprised the final study population for study II (figure 1).

The baseline data from Central Military Hospital medical records of all 232 respondents to the follow-up questionnaire from Asthma Group 1 were collected. The clinical findings of the participants in the follow-up visit were compared with the non-participants. The results of lung function and allergy tests during military service were used as explanatory variables to current asthma severity, which two different chest physicians evaluated based on the follow-up visit.

4.2 Register data used to compare respondents and non-respondents

We used the nationwide registers of the Finnish Social Insurance Institution to obtain information on the non-respondents to the follow-up questionnaire in studies II–IV. We obtained data at group level from respondents and non-respondents of Asthma Group 1 and from Asthma Group 2 without individual level information. We collected the following data: 1) special medication reimbursement rights for asthma medication in 1992 and 2009 (objective data on reversible bronchial obstruction and the typical symptoms of persistent asthma must be demonstrated in order to obtain the reimbursement rights, see Saarinen et al. 2003 for details of the definition and criteria of these rights), 2) asthma medication purchases in 2008, 3) the number of sick leave periods due to respiratory illness lasting over nine days of 2009. The Finnish Social Insurance Institution provides compensation for an employer when sick leave lasts over nine days, therefore those with a shorter period are not found in the register.

4.3 Clinical methods

In study I, clinical investigations were carried out at the Central Military Hospital in 2004–05. In study II, the subjects were examined at baseline (1987–1990) at the Central Military Hospital and at follow up (2009–2010) at the Finnish Institute of Occupational Health.

4.3.1 Lung function tests

Spirometry

Ventilatory function was measured by a flow-volume spirometer (study I: Jaeger Masterlab spirometer, study II: on baseline Pneumoscreen, Eric Jaeger, Germany and at follow-up Medikro) according to the guidelines valid at the time of the studies (study I: ATS 1995, study II at baseline: ATS 1987 and study II at follow-up: Miller et al. 2005). We used the predicted values for the Finnish population (Viljanen 1982). The cut-

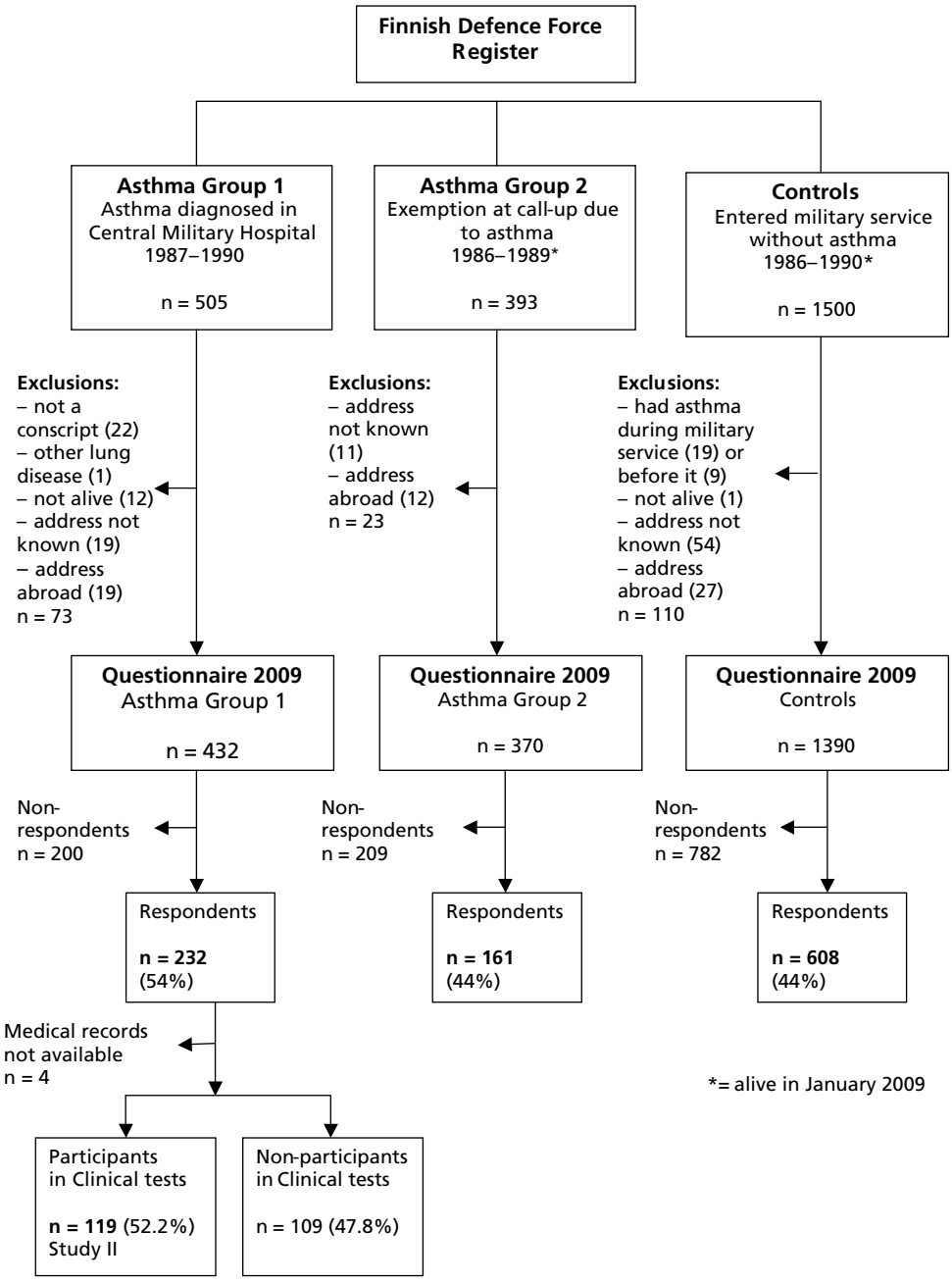

Figure 1. Description of the study populations in studies II–IV

off values for decreased spirometric parameters were based on the lower limits of normal, and were for FEV_1% below 81% of predicted, FEV_1/FVC% below 88% of predicted, and $FEF_{50\%}$ below 62% of predicted . A significant reversibility of airway obstruction was defined as an increase of at least 12% and 200ml in FEV_1 after bronchodilator administration.

Exercise test

A standardised field exercise test was performed using an eight minute free-running test outdoors on a 150 metre circular track between 9 and 11 a.m. (Karjalainen 1991). The running speed was adjusted by monitoring the subject's heart rate with a Sport Tester ™ PE 3000 heart rate meter (Polar Electro Ky, Kempele, Finland). Subjects raised their heart rate to 85% of the predicted maximal rate during a two minute warm up and maintained that level for the remaining six minutes of the test. The PEF values were measured just before the exercise and immediately, 5, 10, 20 and 30 minutes after the exercise. Of the three successive PEF measurements obtained on each occasion, the highest value was recorded for analysis. A positive exercise reaction was defined by at least 15% PEF fall in the 30-minute follow-up after exercise. The response to exercise challenge was the maximum percentage fall in PEF (ΔPEF%) after exercise: % fall in PEF = [PEF(baseline) –PEF(after)]/ PEF(baseline) x100]. Air temperature ranged from –19°C to + 24°C, mean 5.4°C. Therefore, for all exercise challenges, ΔPEF% was adjusted to temperature of 5.4°C by using regression coefficient (–0.327) between air temperature (°C) and ΔPEF% as has been done in a previous study (Rouhos et al. 2005). The regression coefficient was obtained by a linear regression from similar outdoor exercise tests in 1809 conscripts with asthma (Latvala et al. 2000). Those exercise tests were performed during years 1985–1998 in temperatures ranging from –25°C to +26°C.

Histamine challenge

In study I the airway hyperresponsiveness to histamine was assessed using Sovijarvi's method (Sovijarvi et al. 1993) and in study II according to Laitinen's method (Laitinen 1975). It was classified as severe if the concentration of histamine causing a 15% decrease in the FEV_1 values

(PD_{15}) was ≤ 0.10 mg, moderate for PD_{15} values of 0.11 to 0.39 mg, and mild for PD_{15} values of 0.40 to 1.60 mg. In some subjects the reaction was followed up with use of manual PEF meter and then the PEF values were used instead of FEV_1 values.

Serial PEF recording

Serial PEF recordings showing either a diurnal variation of ≥ 20% or a bronchodilatation effect of ≥ 15% at least three times during two weeks period were considered diagnostic for asthma.

4.3.2 Skin prick tests

At baseline skin prick tests (SPT) were performed using both a negative and positive control and a panel of 10 common perennial and seasonal allergens with standardised allergen extracts (ALK). During the follow-up, tests were done with corresponding allergen extracts (ALK-Abello) and positive and negative controls. In case of dermographismus (the negative control ≥ 2mm) the subject's skin prick tests were not accepted for the evaluation. A wheal diameter of at least 3 mm and at least 50% histamine control in SPT was considered positive.

4.3.3 Definition of atopy

In study 1 definition of atopy was based on skin-prick testing in 110 subjects. A subject was considered atopic when at least one positive skin test to common allergens was present. Subjects who reacted to at least four allergens were classified as having multiple sensitisations. If prick tests were missing or showed a dermografismus reaction, then subjects diagnosed with an allergic rhinitis or conjunctivitis by a doctor (n = 18), or a reliable anamnesis of positive skin prick tests (n = 12) were considered to be atopic. In six subjects the atopy status remained undefined.

4.3.4 Other measurements

Blood eosinophils were counted in a Bůrker counting chamber. *Total serum IgE* was measured by solid phase immunoassay, and a concentra-

tion of ≤ 110ku/l was considered normal. *BMI* was calculated as weight in kilograms divided by the square of height in metres, from measured height and weight during military service (studies I and III) and from self-reported measures at follow-up. Overweight was defined as a BMI ≥ 25 kg/m^2 and being obese as a BMI ≥ 30 kg/m^2.

4.4 Questionnaire

In studies I, III and IV we used the previously validated Finnish questions of the Tuohilampi questionnaire to evaluate current asthma symptoms and their frequency, the presence of other atopic disorders, the current use of asthma medication and the age of asthma onset (Kilpelainen et al. 2001). Data was collected on personal characteristics, asthma history and family history, asthma symptoms and their frequency, use of asthma medication, lifestyle, weight, height, occupational and domestic exposures and social situation.

In studies III and IV, questions on, education, lifetime work history, current exposure at work, aggravation of asthma symptoms at work and work ability were included. Classification of asthma was based partly on the questionnaire data, while assessment of work ability and occupational exposure was based solely on the questionnaire. The details of the classifications for these variables are presented in the following chapters.

4.4.1 Basic characteristics

Education: Subjects having completed only comprehensive school, high school or vocational school were classified as having basic education. Those with college or other upper secondary education were classified as having mid-level education. Subjects with a university degree were classified accordingly (http://www.stat.fi/meta/kas/koulutusaste.html.).

Professional status was categorised as self-employed or farmer, upper level non-manual worker, lower level non-manual worker, manual worker, and other or unknown (http://www.stat.fi/meta/luokitukset/sosioekon_asema/001-1989/index.html).

Smoking. According to the questionnaire data, the respondents were classified as current smokers, ex-smokers or non-smokers.

Alcohol consumption. Subjects who reported drinking six or more standard units of alcohol (Brick 2006) at a time once a week or more often were categorized as frequently consuming multiple alcohol units.

Physical activity. Those who reported taking part in exercise that results in at least mild breathlessness and sweating for at least half an hour at a time, only once a week or less in their free time, were classified as physically inactive.

4.4.2 Release of asthma symptoms on days off

The question: "Are your asthma symptoms releasing on days off?" was used. The answers yes, frequently or yes, sometimes were defined to have indicate a release of asthma symptoms on days off. In the risk factor analyses these subjects were compared with those choosing the answer alternative "no". The subjects reporting that they did not have asthma symptoms at all during current job were excluded from the risk factor analyses.

4.5 Classification of asthma

4.5.1 Asthma severity

Study II

In study II, we used the GINA 2002 guidelines (GINA 2002) to evaluate current asthma severity at the follow-up visit. Two independent GINA classifications were combined, the first based on symptoms and FEV_1 and the second on current medication, in order to construct a final "symptom-FEV_1-medication" classification as described earlier (Liard et al. 2000) and in table 5. Clinical severity was classified as one of four grades according to the frequency of diurnal and nocturnal symptoms in the last 12 months and the prebronchodilator FEV_1 of predicted values. Treatment was also classifiedinto one of four grades, according to reported daily medication use. Finally, asthma severity was based on the independent classifications of clinical severity and medication, according to GINA. The following categories were used: remission, intermittent, mild persistent, moderate persistent and severe persistent. Remission was defined as having no asthma symptoms and using no asthma medication

for the last three years. Classification was carried out by two physicians (I. Lindström and H. Suojalehto) separately, and the results proved congruent with each other. The kappa coefficient between the two observations was 0.90. If these two classifications differed from each other, then the asthma severity evaluation of I. Lindström was used.

In study II, baseline asthma severity was evaluated according to modified GINA guidelines and classified as intermittent, mild persistent or moderate/severe persistent. Treatment step classes were not used, because most subjects had no treatment, and the medication used differed from the current treatment guidelines.

Studies I, III and IV

In studies I, III and IV, we evaluated asthma severity based on the questionnaire data and used validated questions concerning frequency of various asthma symptoms and the use of medication during last 12–36 months. We used the GINA 2002 classification as in study II, but we carried out the asthma severity evaluation without FEV_1 values. Such a GINA classification without spirometry data has been used in previous studies (Taylor et al. 2008b). A chest physician (I. Lindström) made the classifications. Remission of asthma was defined as no attacks of shortness of breath with wheezing, no cough with wheezing, and no use of asthma medication during the last 12 months in study I and during the last 3 years in studies III and IV.

4.5.2 Asthma control

We used ACT (Finnish version of the Asthma Control Test™. The Asthma Control Test™ is a trademark of Quality Metric Incorporated © 2002 GlaxoSmithKline) to evaluate current asthma control (Nathan et al. 2004) in study IV. This self-administered questionnaire assesses key components of asthma control over the prior 4 weeks, including asthma symptoms, everyday functioning, use of rescue medications, and night time awakenings. The ACT scale ranges from 5 to 25, with higher scores indicating better asthma control and subjects having a score less than 20 are identified to have poorly controlled asthma. The subjects having a score of ≥ 20 are thought to have well-controlled asthma.

Table 5. Asthma severity evaluation based on GINA 2002. The severity was evaluated by combining the current severity of the asthma treatment (horizontal axis) and the current severity of asthma based on symptoms and lung function (vertical axis).

	Current treatment step			
	Intermittent Only when needed	Mild Persistent ICS ≤ 800μg/day** or leucotriene modifier	Moderate persistent ICS > 800μg/day** or inhaled corticosteroid 100–800μg/day plus long-acting inhaled $\beta_2$agonist or inhaled corticosteroid 100–800μg/day plus leucotriene modifier/ theophylline	Severe persistent ICS ≥ 1000μg/day ** with or without long-acting inhaled $\beta_2$agonist plus one or more of the following if needed: – theophylline – leukotriene modifier – oral corticosteroid
Symptoms and lung function*	**Definitive severity**			
Intermittent – Symptoms < once a week – Nocturnal symptoms ≤ twice a month – FEV_1≥80% – PEF variability < 20%	Intermittent	Mild Persistent	Moderate Persistent	Severe persistent
Mild persistent – Symptoms ≥ once a week but < once a day – nocturnal symptoms > twice a month but ≤ once a week – FEV_1≥80% – PEF variability 20–30%	Mild Persistent	Moderate Persistent	Severe Persistent	Severe Persistent

	Current treatment step			
	Intermittent	Mild Persistent	Moderate persistent	Severe persistent
Moderate persistent – daily – nocturnal symptoms > once a week – 60% < FEV_1 < 80% – PEF variability > 30%	Moderate Persistent	Severe Persistent	Severe Persistent	Severe Persistent
Severe persistent – frequent exacerbations – frequent nocturnal asthma symptoms – limitation of physical activities – $FEV_1 \leq 60\%$ – PEF variability > 30%	Severe Persistent	Severe Persistent	Severe persistent	Severe Persistent

* = worst feature determines severity classification
** = doses of inhaled corticosteroids are equivalent to Beclomethasone dipropionate

ICS = inhaled corticosteroid
FEV_1 = forced expiratory volume in one second
PEF = peak expiratory flow

4.5.3 Occurrence of exacerbations

The subjects were classified as having an asthma exacerbation, if they reported at least one of the following during the last 12 months: 1) an unscheduled office visit or an emergency department visit for asthma, 2) a hospitalisation for asthma or 3) an oral corticosteroid burst for asthma.

4.6 Assessment of work ability

4.6.1 Self-assessed work ability

We used the Work Ability Index (WAI) in assessing current work ability (Tuomi et al. 2006). The WAI is based on series of questions that take into consideration the physical and mental demands of work and the health resources of the worker. Due to the relatively young age of the population studied we used only five first questions of the WAI and left out several questions about chronic diseases. The participants were asked to compare their current work ability with their best lifetime work ability so that 0 represented full work disability and 10 indicated work ability at its best. This validated question was the main indicator for self-assessed work ability, and belonged to the Work Ability Index (WAI) questionnaire as did all other questions about self-assessed work ability (Tuomi et al. 2006). The subjects with current work ability ≤ 7 compared with lifetime best were classified as having decreased work ability, and those with values of 8–10 as having normal work ability. Based on Finnish Health 2000 Survey, 88% of men in the entire Finnish population aged 30–44 had a work ability of 8–10 compared with lifetime best (Gould et al. 2008).

4.6.2 Participation in work life

The subjects were asked if they were currently full-time employed, part-time employed, unemployed, temporarily dismissed, studying, on sick leave, on disability pension, on another pension, or if they took care of households or children. As it was possible to choose many alternatives, the answers were classified by selecting the following groups in the following order: 1. The men who answered that they were either full-time or part-time employed were by default classified as employed, 2. The men who answered that they were unemployed or on temporary dismissal were classified as unemployed, 3. Those who answered that they received disability pension were classified as on disability pension, and 4. All the rest were classified as being temporarily out of work for other reasons. The subjects classified as unemployed, on disability pension or temporarily out of work for other reasons were defined as not employed. Informa-

tion on ever having been unemployed or having changed occupation after military service and the number of such periods was also elicited.

4.7 Workplace exposure

4.7.1 Self-reported

The respondents were asked about exposure to each of the following factors in their current job using previously established questions: dusts, chemical agents or factors, abnormal temperatures (cold and heat), poor indoor air quality, mental stress, and physically strenuous work (Saarinen et al. 2003).

4.7.2 Job exposure matrix

The current or last occupation of the respondents was first coded according to the 1997 Classification of Occupations of Statistics Finland (Käsikirjoja 14 (Handbook 14). Helsinki 1997), which is based on the European Community revision of the International Standard Classification of Occupations (ISCO-88 (COM)). The coded occupational history was matched with the asthma specific JEM developed by Kennedy et al (Kennedy et al. 2000) in order to assign the study subjects to exposure risk groups based on ever having had a job that places them at high risk of developing OA or having been exposed to some other non-specific respiratory irritants. The asthmogens were classified into three groups as follows: high-molecular-weight agents (HMW), low-molecular-weight agents (LMW) or mixed environment; and the non-asthmogenic irritants were grouped into one separate group, as in the previous study (Le Moual et al 2005). Latex exposure was ignored in our study, as non-powdered low-latex gloves have been used in Finland for many years.

4.8 Statistical methods

Our data set consisted of both continuous and categorical variables. When exploring relationships between variables we applied Chi-squared tests for categorical variables. In the same way, one-way ANOVA was

used for continuous normally distributed variables and Kruskal-Wallis for continuous non-normally distributed variables. A p-value of < 0.05 was considered statistically significant. We used logistic regression analyses for examining the associations between explanatory determinants and current persistent asthma in study II, decreased work ability at follow-up in study III and poorly controlled asthma/asthma exacerbations/current asthma severity in study IV. The ORs with 95%CI are presented.

All analyses were carried out using the Statistical Analysis System 9.1 programme (SAS Institute Cary, USA).

4.9 Ethics

The study was approved by the Ethical Committee of the Department of Medicine of Helsinki University Central Hospital. Written informed consent was obtained from the study subjects in studies I–IV.

5 RESULTS

5.1 Asthma prognosis of young male conscripts

5.1.1 Short-term prognosis (study I)

The mean age of the subjects was 19.7 years at baseline and 22.4 years at follow-up and approximately 75% of the patients were atopic. Two groups of asthmatics were identified: those who already had asthma when entering the military service (n = 71, 48.6%) and those, who had a new-onset asthma during service (n = 75, 51.4%). The subjects who had asthma before military service were more frequently sensitised in skin prick tests (p = 0.017) and reported higher prevalence physician-diagnosed allergic conjunctivitis (p = 0.020), allergic rhinitis (p = 0.008) and atopic eczema (0.145) than those suffering from new-onset asthma.

At baseline, asthma was intermittent in 4% of men, mild persistent in 26% of men, moderate persistent in 69% and severe persistent in 0.7% of men. The age of onset tended to predict asthma severity during military service. Asthma was moderate persistent in 88.9% of the 27 patients whose asthma had been confirmed under seven years of age, compared with 72.5% and 62.3% of study members who had been diagnosed at the age of 7–18 and over 18 years respectively (p = 0.108). At follow-up, asthma was in remission in 19.7%, mild intermittent in 41.8%, mild persistent in 22.6%, and moderate persistent in 15.6%. Overall asthma was less severe at two year follow-up than during military service (p = 0.036). Both during military service and at two-year follow-up, asthma was milder among the men, who had a new-onset asthma during military service.

Atopy (p = 0.002), number of positive skin prick tests (p = 0.005) and higher total serum IgE (p = 0.001) at baseline were significant predictors for more severe asthma at follow-up.

5.1.2 Long-term prognosis (study II)

We found no statistically significant differences in baseline characteristics of study participants and those 109 subjects, who answered the questionnaire without participating in the clinical visit. The characteristics of study participants at baseline and 20-year follow-up are presented in table 6. Asthma was less severe at follow-up than at baseline. At follow-up, 11.8% of the men were in remission, 42.0% had intermittent asthma, 10.9% had mild persistent asthma, and 35.3% had moderate/severe persistent asthma. A total of 56.3% (67) of the subjects had positive exercise test at baseline.

Smoking habits and the results of lung function and allergy tests during military service were used as explanatory variables for current asthma severity. Smoking (p = 0.050), decreased FEV_1% predicted (p=0.001), decreased FEV_1/FVC% predicted (p < 0.0001), decreased $FEF_{50\%}$% predicted (p = 0.001), PEF decrease of ≥ 10% in exercise tests (p = 0.011), and more severe asthma (p = 0.028) at baseline showed a statistically significant association with persistent asthma at follow-up. No significant associations were found between asthma severity at follow-up and the age of asthma onset, positive skin prick tests, or airway hyperresponsiveness to histamine at baseline.

We assessed the predictive value of spirometry and exercise test findings at baseline for persistent asthma at follow-up by using univariate and multivariate models. Decreased FEV_1 % predicted, decreased FEV_1/FVC % predicted, decreased $FEF_{50\%}$ % predicted and a positive exercise test (PEF decrease ≥ 15%) at baseline associated with persistent asthma at follow-up (table 7). The risk remained after adjustment for smoking and asthma severity at baseline. In our final multivariate model exercise test results and FEV_1/FVC% predicted results at baseline were adjusted for each other as well as for smoking and asthma severity at baseline (data not shown). In this model the OR for current persistent asthma was 3.2 (95%CI 1.0–9.8) in subjects with a positive exercise test and 4.0 (95%CI 1.7–9.3) in subjects with a decreased FEV_1/FVC ratio.

Table 6. Characteristics of participants at baseline and follow-up in study II. Data provided as % (n) unless otherwise stated.

	Baseline 1987–90 n = 119	Follow-up 2009–10 n = 119	p-value
Age, mean, years, (SD)	20.1 (1.4)	41.2 (1.9)	
Smoking*			0.002
Non-smoker	52.9% (63)	65.5% (78)	
Ex-smoker	10.9 % (13)	14.3 % (17)	
Smoker	36.1 % (43)	20.2 % (24)	
BMI, mean, kg/m², (SD)	22.9 (3.0)	27.7 (5.1)	< 0.001
Skin prick tests*			0.026
0 positive	13.8% (15)	13.6% (16)	
1–3 positive	25.7% (28)	14.4% (17)	
≥ 4 positive	60.5% (66)	72.0% (85)	
Prebronchodilator spirometry*			
FVC % predicted, mean (SD)	98.2 (11.6)	93.7 (11.4)	< 0.001
FEV_1 % predicted, mean (SD)	88.3 (12.0)	88.5 (13.3)	0.827
FEV_1/FVC % predicted, mean (SD)	89.7 (9.6)	94.3 (9.1)	< 0.001
$FEF_{50\%}$ % predicted, mean (SD)	62.7 (16.6)	74.4 (23.9)	< 0.001
Asthma severity			< 0.001
Remission	0% (0)	11.8% (14)	
Intermittent	33.6% (40)	42.0% (50)	
Mild persistent	19.3% (23)	10.9% (13)	
Moderate/severe persistent	47.0% (56)	35.3% (42)	
Using inhaled corticosteroid	0	22.7% (27)	

* = due to some missing data the number of subjects varies from 119.
BMI = body mass index, FVC = forced vital capacity, FEV_1 = forced expiratory volume in 1 second, $FEF_{50\%}$ = forced expiratory flow rate at 50% of vital capacity, PD = provocative dose, PEF = peak expiratory flow, ND = not done, SD = standard deviation

Table 7. Risk of current persistent asthma according to spirometry and exercise test findings at baseline (study II)

Predictors at baseline	Univariate model			Adjusted for smoking and asthma severity at baseline		
	OR	95%CI	p-value	OR	95%CI	p-value
Spirometry, n = 118						
FEV_1 % predicted ≥ 81	1	reference		1	reference	
FEV_1 % predicted < 81	**4.0**	1.7–9.5	0.002	**3.3**	1.3–8.7	0.016
FEV_1/FVC % predicted ≥ 88	1	reference		1	reference	
FEV_1/FVC % predicted < 88	**4.8**	2.2–10.7	< 0.001	**4.0**	1.7–9.1	0.001
$FEF_{50\%}$ % predicted ≥ 62	1	reference		1	reference	
$FEF_{50\%}$ % predicted < 62	**3.5**	1.6–7.5	0.002	**2.8**	1.3–6.4	0.012
Exercise test, n = 119						
PEF decrease < 10%	1	reference		1	reference	
PEF decrease 10.0–14.9%	1.2	0.4–4.1	0.420	1.3	0.4–4.4	0.541
PEF decrease ≥ 15 %	**3.5**	1.3–9.0	0.004	**3.2**	1.1–9.5	0.021

FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, $FEF_{50\%}$ = forced expiratory flow rate at 50% of vital capacity, PEF = peak expiratory flow. Significant OR values are shown in bold.

5.2 Characteristics of the study population in studies III–IV

5.2.1 Characteristics of the study participants

The characteristics of the study groups are presented in table 8. The socioeconomic status of Asthma Group 2 differed from the other groups: these men had a lower educational level and more often worked as manual workers. JEM based exposure to LMW asthmogens in the most recent occupation was more common among the controls, but other differences in occupational exposure could not be found. Asthma was currently more severe in Asthma Group 2. The asthmatics smoked currently slightly more often than the controls. The use of asthma medication based on the questionnaire data is presented in table 9.

Table 8. Characteristics of study population in studies III–IV

	Asthma Group 1 n = 232	Asthma Group 2 n = 161	Controls n = 608	p-value
Mean age, years (SD)	40.9 (1.7)	40.6 (1.9)	41.0 (1.9)	0.048
Smoking				0.252
Non-smoker	41.6 (96)	45.0 (72)	42.8 (259)	
Ex-smoker	22.9 (53)	25.0 (40)	28.8 (174)	
Smoker	35.5 (82)	30.0 (48)	28.4 (172)	
BMI kg/m²				0.153
< 25	29.4 (68)	39.8 (64)	37.3 (223)	
25.0–29.9	47.6 (110)	40.4 (65)	44.5 (266)	
≥ 30.0	22.9 (53)	19.9 (32)	18.2 (109)	
Doctor diagnosed allergic rhinitis	77.6 (177)	82.3 (130)	30.1 (182)	< 0.001
Education				0.032
Basic	57.0 (126)	63.3 (95)	56.2 (320)	
Mid-level	29.9 (66)	24.0 (36)	23.6 (134)	
University	13.1 (29)	12.7 (19)	20.2 (115)	

Continues on next page →

	Asthma Group 1 n = 232	Asthma Group 2 n = 161	Controls n = 608	p-value
Occupation				0.063
Upper-level non-manual worker	25.0 (58)	15.5 (25)	27.9 (169)	
Lower-level non-manual worker	14.2 (33)	14.3 (23)	11.7 (71)	
Manual worker	32.8 (76)	41.0 (66)	35.5 (215)	
Self-employed	18.5 (43)	14.9 (24)	16.7 (101)	
Not currently employed	5.6 (13)	9.9 (16)	5.6 (34)	
Other or unknown	3.9 (9)	4.4 (7)	2.5 (15)	
JEM based occupational exposure*				
HMW asthmogens	3.3 (7)	4.4 (6)	2.6 (14)	0.517
LMW asthmogens	3.8 (8)	5.1 (7)	10.2 (56)	0.006
Mixed environment asthmogens	5.7 (12)	4.4 (6)	8.4 (46)	0.170
Any asthmogen	9.1 (19)	12.3 (17)	15.9 (87)	0.045
Non-asthmogenic irritants	35.7 (75)	31.9 (44)	37.3 (205)	0.486
Self-reported occupational exposure*				
Dust/chemical agents/gases/ fumes	66.7 (140)	74.6 (103)	66.9 (367)	0.192
Abnormal temperatures	42.9 (90)	44.2 (61)	42.3 (232)	0.917
Bad indoor quality	24.3 (51)	23.9 (33)	21.9 (120)	0.727
Physically strenuous work	49.1 (103)	46.4 (64)	49.5 (272)	0.801
Change of occupation ever	67.0 (150)	55.7 (78)	57.1 (338)	0.025
Change of occupation due to asthma				0.430
No	86.2 (188)	83.2 (124)		
Yes, partly	11.5 (25)	12.1 (18)		
Yes, mainly	2.3 (5)	4.7 (7)		

Data is presented as % (n) unless otherwise stated. P-values for χ^2-test for categorical variables and one-way ANOVA for continuous variables
* = The subjects who were not currently employed were excluded (After the exclusions, n = 210 in Asthma Group 1, n = 138 in Asthma Group 2 and n = 549 in Controls)
BMI = body mass index, JEM = asthma specific job exposure matrix, HMW = high molecular weight, LMW = low molecular weight.

Table 9. Use of asthma medication during past 12 months based on the questionnaire data (studies III–IV)

Medication	Asthma Groups 1+2 n = 393*
None	24.4 (96)
Only when needed	34.4 (135)
Only bronchodilator regularly**	2.0 (8)
ICS regularly	18.3 (72)
ICS+LABA regularly	18.3 (72)
Other combination regularly	1.05 (6)

Data is presented as % (n)
* = missing data in 4 subjects
** = regularly means daily or almost daily
ICS = inhaled corticosteroid LABA = long acting bronchodilator

5.2.2 Comparison between respondents and non-respondents

Based on the nationwide registers of the Finnish Social Insurance Institution there were no significant differences between respondents and non-respondents in Asthma Group 1. The respondents of Asthma Group 2 had special medication reimbursement rights for asthma medication statistically significantly more often in 1992 (p = 0.022) and in 2009 (p = 0.007) than non-respondents. We found no significant differences in asthma medication purchased in 2008 or the number of periods of sick leave due to respiratory illness between the respondents and non-respondents of Asthma Group 2.

5.3 The work ability (study III)

5.3.1 Participation in work life and the current self-assessed work ability

A total of 9.2% of the subjects in Asthma Group 1, 14.3% of the subjects in Asthma Group 2, and 9.4% of the controls were not currently employed (p = 0.165) (table 8). Being ever unemployed was most common

among men in Asthma Group 2, while having ever changed occupation was most common in Asthma Group 1.

The asthmatics had reduced self-assessed work ability: current work ability compared with lifetime best was ≤ 7 in 28.9% of Asthma Group 1, in 31.1% of Asthma Group 2, and in 19.7% of the controls (p = 0.0007). Work ability as regards physical job demands was moderate or bad in the groups, at 32.0%, 34.2% and 23.4%, respectively (p = 0.004), and 17.3%, 24.0% and 15.4% (p = 0.037) as regards mental job demands. No significant difference in the mean number of sick leave days during the last 12 months and the self-assessed estimate of work ability two years from baseline were found between the groups.

Table 10. Risk of decreased self-assessed work ability in the univariate and multivariate models (study III)

	Unadjusted		Adjusted with education, professional status and life style factors	
	OR	**95%CI**	**OR**	**95%CI**
Current work ability compared with life time best (≤ 7 vs. 8–10)				
Controls	1	reference	1	reference
Asthma Group 1	1.7	1.2–2.3	1.5	1.0–2.2
Asthma Group 2	1.8	1.2–2.7	1.6	1.0–2.5
Work ability in the relation to physical demands of work (moderate or bad vs. very good or quite good)				
Controls	1	reference	1	reference
Asthma Group 1	1.5	1.1–2.2	1.4	1.0–2.1
Asthma Group 2	1.7	1.2–2.5	1.5	1.0–2.3
Work ability in the relation to mental demands of work (moderate or bad vs. very good or quite good)				
Controls	1	reference	1	reference
Asthma Group 1	1.1	0.8–1.7	1.1	0.7–1.6
Asthma Group 2	1.7	1.1–2.7	1.6	1.1–2.5

* = life style factors consisted of BMI classes, current smoking, frequent use of multiple alcohol doses and physical inactivity

The increased risk of decreased self-assessed work ability remained when adjusted with education, professional status and lifestyle factors in the multivariate models (table 10). Work ability in relation to the mental demands of the work was reduced only in Asthma Group 2.

5.3.2 Risk factors for decreased work ability among asthmatics

In the logistic regression analysis current smoking, only basic education, being a manual worker or being self-employed, and suffering from current severe asthma were most strongly associated with decreased work ability among the asthmatics (table 11). Occupational exposure to nonasthmogenic irritants according to JEM and self-reported occupational exposure to abnormal temperatures were also related to the same outcome. The association with smoking strengthened in the logistic model including all listed variables, while others weakened, becoming no longer significant (data not shown). The term risk factor is used, although the determinants of decreased work ability are measured at the time of follow-up.

Table 11. The odds ratios (ORs) for decreased self-assessed current work ability compared with lifetime best (≤ 7 vs. 8–10) among asthmatics and controls (study III)

Risk factor	Asthma Groups 1 and 2		Controls	
	OR	95%CI	OR	95%CI
Long lasting rhinitis	**1.8**	1.0–3.1	**1.6**	1.1–2.4
Current smoking	**2.5**	1.6–3.9	**1.5**	1.0–2.4
BMI over 30	1.7	0.9–3.0	**2.8**	1.6–4.9
Education				
University	1	reference	1	reference
Mid-level	1.8	0.7–4.3	2.1	1.0–4.4
Basic	**2.6**	1.1–5.8	**3.2**	1.6–6.2
Professional status				
Upper level non-manual worker	1	reference	1	reference
Lower level non-manual worker	1.6	0.7–3.9	1.6	0.7–3.5
Manual worker	**2.7**	1.4–5.6	**2.0**	1.1–3.5
Self-employed	**2.5**	1.1–5.6	1.5	0.7–3.0
Other or unknown	**9.7**	4.1–23.0	**11.4**	5.4–24.1
JEM based occupational exposure				
HMW asthmogens	1.6	0.6–4.6	0.5	0.1–2.4
LMW asthmogens	0.6	0.2–1.9	0.9	0.4–1.7
Mixed environments asthmogens	0.9	0.4–2.5	1.0	0.5–2.0
Any asthmogen	1.1	0.5–2.1	0.8	0.4–1.4
Nonasthmogenetic irritants	**1.7**	1.1–2.7	1.3	0.9–2.0
Self -reported occupational exposure				
Dusts, chemic agents, gases or fumes	1.3	0.8–2.1	1.3	0.8–1.9
Abnormal temperatures	**1.7**	1.1–2.7	1.2	0.8–1.8
Bad indoor air quality	1.6	0.9–2.5	**1.7**	1.1–2.7
Mental stress	1.2	0.8–1.9	1.3	0.8–1.9
Physically strenuous work	0.6	0.4–1.0	0.9	0.6–1.3
Current asthma severity				
Remission (1)	1	reference		
Intermittent (2)	2.1	0.7–6.5		
Mild persistent (3)	1.8	0.5–5.9		
Moderate (4)	2.1	0.6–7.0		
Severe (5)	**3.8**	1.1–13.5		

Statistically significant results are shown in bold. JEM = asthma specific job exposure matrix, HMW = high-molecular-weight agents, LMW = low-molecular-weight agents.

5.4 Work and workplace exposure associations with current asthma status (study IV)

5.4.1 Current asthma control, occurrence of exacerbations and asthma severity

A total of 40.5% of the subjects in the Asthma Group 2 had currently moderate or severe persistent asthma, while only 17.7% of the men in Asthma Group 1 had these severity forms of asthma (table 12). Asthma was also more often uncontrolled in Asthma Group 2 and exacerbations during last 12 months were more frequent.

Table 12. Current asthma status (study IV)

	Asthma Group 1 n = 232	Asthma Group 2 n = 161	p-value
Asthma control			0.002
Well controlled (≥ 20)	85.2 (172)	72.0 (113)	
Poorly controlled (< 20*)	15.1 (30)	28.0 (44)	
Asthma exacerbation during last 12 months			0.036
No	88.4 (205)	80.8 (130)	
Yes	11.6 (27)	19.3 (31)	
Asthma severity**			< 0.001
Remission	8.3 (17)	3.8 (6)	0.0793
Intermittent	58.3 (119)	29.7 (47)	
Mild persistent	15.7 (32)	26.0 (41)	
Moderate persistent	11.8 (24)	24.0 (38)	
Severe persistent	5.9 (12)	16.5 (26)	

Data are presented as % (n) unless otherwise stated. P-values for $\chi 2$ test
* = Asthma Control Test value
** = Based on the modified 2002 GINA-guidelines

5.4.2 Determinants of current poor asthma outcome

In the univariate model (data not shown) current smoking was associated with poorly controlled asthma in Asthma Group 1 (OR 3.6, 95%CI 1.4–9.3) and in Asthma Group 2 (OR 2.5, 95%CI 1.1–5.5), whereas asthma exacerbations did not significantly correlate with smoking. In the smoking adjusted model (current smoker vs. ex-/non-smoker) Asthma Group 1 (men with mild/moderate asthma in youth) and Asthma Group 2 (men with relatively severe asthma in youth) are analysed separately using logistic regression.

Poorly controlled asthma

Being obese (OR 4.2, 95%CI 1.2–14.9) was significantly associated with poorly controlled asthma in Asthma Group 1. Not being currently employed yielded an OR of 3.5 (95%CI 1.1–11.0) and relief of asthma symptoms on days off an OR of 2.4 (95%CI 1.0–5.7) for currently poorly controlled asthma in Asthma Group 2.

Occurrence of asthma exacerbations

Obesity and educational level showed no statistically significant associations with asthma exacerbations in past 12 months. In Asthma Group 2, being a manual worker/self-employed (OR 4.5, 95%CI 1.2–16.3) and not being currently employed (OR 4.9, 95%CI 1.1–22.3) was significantly associated with asthma exacerbations (table 13). Self-reported occupational exposure to asthma aggravating factors showed a clear tendency to associate with exacerbations in Asthma Group 2, with ORs between 2.0 and 3.5. However they had no statistical significance. We also detected some tendency of association between JEM-based exposure to non-asthmogenic irritants and asthma exacerbations.

Table 13. Determinants of occurrence of exacerbations studied with smoking adjusted model (study IV)

Determinants at follow-up	Asthma exacerbations			
	Asthma Group 1 n = 27		Asthma Group 2 n = 31	
	OR	95%CI	OR	95%CI
Occupation				
Non-manual worker	1	reference	1	reference
Manual worker/self-employed	0.7	0.3–1.7	**4.5**	1.2–16.3
Not employed/other/unknown	1.1	0.3–4.2	**4.9**	1.1–22.3
JEM-based occupational exposure in current job*				
Any asthmogen -no	1	reference	1	reference
Any asthmogen -yes	0.4	0.1–3.5	0.6	0.1–2.7
Non-asthmogenic irritants -no	1	reference	1	reference
Non-asthmogenic irritants -yes	0.6	0.2–1.8	1.6	0.6–3.9
Self-reported occupational exposure in current job*				
Dust/chemical agents/gases/ fumes -no	1	reference	1	reference
Dust/chemical agents/gases/ fumes -yes	0.7	0.3–1.9	3.5	0.8–16.6
Abnormal temperatures -no	1	reference	1	reference
Abnormal temperatures -yes	0.7	0.3–1.8	2.0	0.8–5.0
Poor indoor quality -no	1	reference	1	reference
Poor indoor quality -yes	1.3	0.5–3.7	2.2	0.8–5.7
Physically strenuous work -no	1	reference	1	reference
Physically strenuous work -yes	0.9	0.4–2.2	2.2	0.8–5.8

Significant OR values are shown in bold. This model is smoking adjusted (current smoker vs. ex-smoker or non-smoker). Other adjustments were not made, because all study participants were male and of the same age, and occupational exposure-related variables correlated closely with each other and with the educational level.
* = Participants who were not currently employed or had changed jobs in 2008 or 2009 were excluded from the analysis (44 participants in Asthma Group 1 and 37 participants in Asthma Group 2). After the exclusion, 20 participants in Asthma Group 1 and 24 in Asthma Group 2 had asthma exacerbations.
JEM = asthma specific job exposure matrix, CI = confidence interval

Moderate or severe persistent asthma

We also analysed associations between current moderate or severe persistent asthma and all the listed variables in table 13, educational level and obesity (data not shown). We found no significant associations.

6 DISCUSSION

6.1 Study population and methods

6.1.1 Study population

We used the Finnish Defence Forces registers to select the study populations. In studies I and II, we selected the populations from the Register of Central Military Hospital, while in studies III–IV we also included data from a nationwide register, which has been used in earlier studies (Haahtela et al. 1990; Latvala et al. 2005). Our study subjects represented mainly men with the early onset atopic asthma -phenotype (Pavord 2012) and therefore our results are restricted to this asthma type.

Study I

In study I, all 216 men with verified asthma in 2004–2005 from the register of the Central Military Hospital were included in the study base. These subjects represented a population of men with mild or moderate asthma aged 18–27, from southern and central parts of Finland. This population was homogenous as regards age and sex. The response rate was fairly high (68%). We limited our study to those men whose asthma was aggravated to such an extent that they were referred for a clinical evaluation in a pulmonary medicine unit. In 2004 and 2005 altogether about 55 000 young men aged around 20 started their military service in Finland. The prevalence of ever having had asthma before that age can be estimated to be about 6% in those men. Thus one can conclude that the majority of young men with an asthma history could complete their service without being referred for a clinical evaluation. No conclusions can be drawn on the prognosis of such cases of asthma.

Studies II–IV

In the studies II–IV, the study population was homogenous as regards age and sex and represented unselected men from Southern and Central parts of Finland. The asthma groups had a clinically verified disease at the age of 19–21 and represented various severity forms of asthma, while the control group had no asthma in youth. The asthma severity in youth of all asthmatics could be roughly evaluated based on the Defence Forces exemption criteria from military service. We identified two groups of asthmatics: *recruits with asthma* (Asthma Group 1) and *asthmatics exempted from service* (Asthma Group 2). This longitudinal setting allowed us to study associations between asthma lasting at least 20 years and work ability as well as current asthma status. Although our results cannot be generalised to females or asthma starting later, the work ability of this subgroup of asthmatics as well as associations between workplace exposure and asthma are essential. These asthmatics have suffered from asthma for their entire or almost entire career and being male they are more likely to work in dusty workplaces. Furthermore most of the men we studied have had asthma since the age, when career choices are usually made.

The limitation of this study was the low response rate and the further non-participation of many subjects in the clinical follow-up visit. Based on the nationwide registers of the Finnish Social Insurance Institution on asthma medication and sick leave: 1) no significant differences between respondents and non-respondents in *recruits with asthma* were found and 2) no significant differences between respondents and non-respondents in *asthmatics exempted from service* in asthma medication purchased in 2008 or the number of periods of sick leave due to respiratory illness were found. We proved neither a statistically significant difference in baseline characteristics of men participating clinical follow-up visit and men, who answered the questionnaire without participating the clinical visit. However the possibility of selection bias cannot be ruled out. In questionnaire studies it is common for men in younger age-groups not to respond. A recent Swedish study with a male response rate of 56% showed no difference in respiratory symptoms between responders and non-responders (Ronmark et al. 2009).

HWE (Le Moual et al. 2008) is possible in this type of setting and may have led to an underestimation of associations between occupational exposures and asthma as well as work ability. As a large proportion of men in our study suffered from asthma already when career choices were made, one could expect that asthma could lead the asthmatics to choose less exposed jobs. However, in our study, current occupational exposure to asthma aggravating factors based on asthma-JEM and self-reports differed only slightly between the asthmatics and the control group. A change in occupation was most common in *recruits with asthma* ie. those with a later onset of the disease. Due to the 20 year follow-up we evaluated only occupations at the age of around 40 years, while Dumas et al studied first occupational choices and reported that the subjects having more severe asthma in childhood tended to choose less exposed jobs (Dumas et al. 2011).

One interesting finding was the lower socioeconomic status of *asthmatics exempted from service* i.e. those with more severe asthma in youth, when compared with *recruits with asthma* and controls. These men also currently had more severe asthma. The link between more severe asthma and low socioeconomic status has previously been shown among children (Almqvist et al. 2005) and adults (Bacon et al. 2009). The lower socioeconomic status of *asthmatics exempted from service* may have affected their work ability and the exposure to asthma aggravating factors in their current job.

Smoking was as common among the asthmatics as among the controls and associated with decreased work ability and poorer asthma outcome, which is in line with earlier reports (Ulrik 1999; Eisner et al. 2006; Laforest et al. 2006; McLeish et al. 2010). Based on the Finnish guidelines "all health care workers should register smoking among patients, urge them to quit and offer help in cessation" (Tobacco dependence and cessation: Current Care guideline, 2012) and asthmatics in particular should be encouraged to stop (Asthma: Current Care guideline, 2012). Therefore, the high number of smoking asthmatics in our study is of concern and disappointing as regards many health educational programmes.

6.1.2 Methods

Lung function tests

In studies I and II we used the results of lung function tests and allergy tests as predictors for current asthma status. All lung function tests at baseline were performed by qualified technicians with uniform and validated methods in the clinical physiology laboratory of the Central Military Hospital, which had strict quality control procedures. The repeatability of measurements was always controlled according to the guidelines (ATS 1987; ATS 1995; Miller et al. 2005) and measurements with too large a variability were not accepted.

In studies I and II, we used at baseline both a histamine challenge and exercise test in measuring airway hyperresponsiveness. Exercise tests have shown to have higher specificity, but lower sensitivity in diagnosing asthma in comparative studies of these tests (Cockcroft 2010). In another study, adding the inhalation of cold air increased the sensitivity of the exercise test, while still maintaining specificity (Carlsen et al. 1998). The severity of exercise-induced bronchocontriction depends on the level of ventilation and on the temperature of the inspired air. Thus, the exercise tests in this study were heart-rate conducted and temperature adjustments for PEF calculations were included, as Rouhos et al. described in an earlier study (Rouhos et al. 2005). Despite temperature adjustments, the complex effect of the season on the exercise test results cannot be ruled out, because exercise tests were performed outdoors in all seasons. Karjalainen et al demonstrated aggravated exercise-induced asthma response in asthmatics with pollen allergy, when the outdoor exercise test was performed during the pollen season rather than in wintertime (Karjalainen et al. 1989). However, subjects with non-allergic asthma had diminished exercise-induced bronchoconstriction in spring time probably due to more humid, warmer weather. Goldberg et al. reported a lower proportion of positive exercise test results during the summer than in other seasons, and suggested that this was related to the lower activity of asthma during the summer (Goldberg et al. 2005). However this study is from Israel, where, contrary to Finland, summer is not a pollen season. The other limitation in our study was the use of manual PEF-meter and PEF values instead of spirometric FEV_1 in the evaluation of exercise reaction.

Assessment of asthma severity

Assessment of asthma severity is complex and lacks a golden standard suitable for epidemiological studies. In our studies we used the 2002 GINA severity classification, which combines parameters of asthma treatment, lung function and frequency of asthma symptoms (GINA 2002). The 2002 GINA severity classification has been used in epidemiological studies and it has been held as a good determinant of asthma morbidity (Liard et al. 2000; Limb et al. 2005; de Marco et al. 2006; Cazzoletti et al. 2010). Due to the complexity of this classification it is poorly suited to clinical practice and may be also difficult in epidemiological studies (Taylor et al. 2008a). In our study II, two chest physicians classified the asthma severity separately using GINA 2002 classification. These classifications proved congruent with each other having the kappa coefficient between the two observations 0.90. In studies I, III and IV, we carried out current severity assessment without FEV_1, as has been done previously (Taylor et al. 2008b). This might have led to underestimation of asthma severity rather than overestimation. Previously bronchial hyperresponsiviness and airway inflammation were observed despite a clinically apparent remission of asthma (van Den Toorn et al. 2000).

Based on recent recommendations, asthma severity should be classified on the basis of the intensity of treatment required to achieve good asthma control (GINA 2012). "This concept is appropriate for patients who have access to optimal drug treatments and to evaluate the response of patients to these interventions", as WHO Consultation –document summarises (Bousquet et al 2010). In epidemiological population studies, as in our study, this type of severity classifications is difficult because many patients are undertreated based on treatment guidelines. It is also noteworthy that control usually refers to events occurring recently, whereas severity refers to those occurring over a longer period (6–12 months) (Bousquet et al 2010). In our study the severity classification was based on the asthma morbidity during the previous 12 months and took account both the severity of disease and its response to the treatment, although it differed from the current recommendation (GINA 2012). The majority of asthmatics in our study had the atopic phenotype which typically has concordance between symptoms, inflammation and lung function as well as a good response to ICS, Therefore the GINA 2002 severity classification may have been particularly suitable for our study.

Assessment of work ability

The diverse nature of work ability makes its definition and measurement a challenge. As the age of the population studied has a remarkable effect on the work ability (Gould et al 2008), the indicators of severe forms of work disability, like disability pension or long-term sick leave were not appropriate in our study with relatively young participants.

We used the Work Ability Index (WAI) in assessment of current work ability. WAI has been developed in a follow-up study that involved ageing municipal workers in different types of occupations (Ilmarinen et al. 1997; Tuomi et al. 2006). The WAI is based on a series of questions that take into consideration the physical and mental demands of work and the health resources of the worker. The internal validity of WAI has shown a satisfactory relationship between the subjects' WAI results and more objective measurements (Eskelinen et al. 1991; Nygard et al. 1991) and the test-retest reliability has proved to be good (de Zwart et al. 2002). Our main indicator of work ability was the single question of current work ability compared with lifetime best on a scale of 0–10. This question has appeared to have a strong association with the whole WAI and predict the future degree of sick leave (Ahlstrom et al. 2010).

Assessment of occupational exposure

In our study the occupational exposure evaluation was based on self-reports and the asthma specific JEM developed by Kennedy et al (Kennedy et al. 2000). The former is subject to reporting bias (de Vocht et al. 2005), while the latter is subject to classification bias. One limitation in our study was that we were not able to evaluate the occupational exposure during the whole career. The whole working history was included in the questionnaire, but due to a significant amount of missing and conflicting data we were not able to obtain reliable information.

6.2 Main results

6.2.1 Majority of asthmatics have mild disease

In study I, we found that asthma was significantly less severe two years after military service than during it and over 60% of the participants had remitted or intermittent asthma based on the questionnaire. Subjects with new-onset asthma during military service had less atopic characteristics and also milder asthma at the two-year follow-up. Earlier studies have demonstrated an increased frequency of asthma exacerbation among recruits who already have the disease, and new-onset asthma was associated with military service in combat units (Katz et al. 1999). However, only limited knowledge about asthma prognosis after military service exists.

In study II, based on the clinical data of 119 men with asthma since youth, 11.8% of the men were in remission, 42.0% had intermittent asthma, 10.9% had mild persistent asthma, and 35.3% had moderate/severe persistent asthma at around 40 years of age. This distribution of asthma severity is in line with that of the ECRHS II, where in the follow-up cohort 11.9% were in remission, 45.3% had intermittent asthma, 8.1% mild persistent asthma and 34.7% moderate/severe persistent asthma (de Marco et al. 2006). Both in the ECRHS II and in our study, asthma severity classification was based on GINA 2002 and the mean age of study population was around 40 years. Our study population consisted of men only, but Raherison et al reported no gender difference in asthma severity in the ECRHS II (Raherison et al. 2009). In the follow-up part of OLIN study a higher proportion of participants had more severe forms of asthma. However in that study only subjects who developed asthma after the age of 20 years were included (Ronmark et al. 2007).

In study IV, based on the questionnaire data of 393 asthmatics, 15% of men in *recruits with asthma* and 28% of the men in *asthmatics exempted from service* had poorly controlled asthma based on the ACT scores. Earlier population-based studies have reported a higher proportion of asthmatics having uncontrolled disease (de Marco et al. 2003; Rabe et al. 2004; Peters et al. 2007). For example, in ERCHS II some 66% of participants had poorly controlled asthma (Cazzoletti et al. 2007). These differences between our results and other studies can be explained by the fact that significant proportion of the asthmatics in our study had remitted or intermittent disease.

6.2.2 Predictors of persistent asthma

More severe asthma at baseline was a clear predictor of persistent asthma short-term (study I) and long-term (study II). Furthermore based on our questionnaire data those (studies III–IV) men who were exempted from military service, i.e. had roughly evaluated more severe disease in youth, currently also had a more severe form of the disease compared to subjects belonging to *recruits with asthma* -group at baseline. The severity of childhood asthma has also been shown to predict asthma severity in adulthood in an earlier study (Limb et al. 2005).

Atopy, number of positive skin prick tests, and total serum IgE was significantly associated with persistent asthma in 2-year follow-up. Several earlier studies have linked presence of allergic sensitisation to the persistence of asthma from childhood to adulthood (Sears et al. 2003; Guerra et al. 2004; Limb et al. 2005; Taylor et al. 2005). In the ECRHS studies sensitisation to outdoor moulds, atopy and higher IgE levels have been associated with more severe forms of asthma (Zureik et al. 2002; de Marco et al. 2006; Cazzoletti et al. 2010).

A decreased FEV_1 and a decreased FEV_1/FVC ratio in prebronchodilator spirometry was significantly associated with current persistent asthma 20-year later. Many earlier studies have associated obstructive spirometry, for example, a decreased FEV_1/FVC ratio in asthmatic children, with poorer asthma prognosis (Rasmussen et al. 2002; Sears et al. 2003; Toelle et al. 2004; Vonk et al. 2004). In adult studies, a decreased FEV_1 has predicted more severe asthma later (Panhuysen et al. 1997; de Marco et al. 2006).

In addition to other spirometry parameters, a *decreased $FEF_{50\%}$* at baseline was associated with persistent asthma at follow-up. $FEF_{25–75\%}$ and $FEF_{50\%}$ are the spirometric variables most commonly cited as indicators of small airway obstruction. Although small airways have been linked to recurrent exacerbations of asthma (in 't Veen et al. 2000), nocturnal asthma (Lehtimaki et al. 2002) and also milder asthma (Beigelman-Aubry et al. 2002), there are only a few longitudinal studies related to small airways (van Veen et al. 2008).

A *positive exercise* test was associated with asthma persistence 20 years later in our study, but airway hyperresponsiveness to a histamine challenge had no effect on asthma prognosis. About three quarters of study subjects underwent a histamine challenge, while all of them underwent

the exercise test. The histamine challenge was not performed on some subjects due to obstructive spirometry and thismay affect its predictive value. Airway hyperresponsiveness to metacholine or histamine in childhood has previously been connected to the persistence of asthma symptoms or their onset in adult life (Sears et al. 2003; Toelle et al. 2004). Moreover, less severe airway hyperresponsiveness has been associated with the development of irreversible airflow limitation (Vonk et al. 2003). Little is known about the effect of positive exercise tests on the long-term prognosis of asthma, although exercise-related respiratory symptoms have predicted persistence of asthma in children (Frank et al. 2007).

6.2.3 Reduced work ability in men with asthma since youth

We found that asthma which begins in childhood or early adulthood is associated with a reduction of self-assessed work ability in men around the age of 40. Our first asthma group had mild to moderate asthma, and the second relatively severe asthma in their youth. We compared the work ability of these groups with that of the controls without asthma in youth. The self-assessed work ability compared with lifetime best and work ability as regards physical job demands were reduced in both *recruits with asthma* and *asthmatics exempted from service* even when taking into account the confounders. Work ability in relation to the mental demands of the work was reduced only in *asthmatics exempted from service.* These results seem to make sense, because physical exertion may increase asthma symptoms and thus may have an effect on work ability as regards of physical job demands even in subjects with mild asthma.

Several aspects support considering that the observed reduction of work ability of the asthmatics is important from socioeconomic perspective. Firstly, asthma is a common disease with increasing incidence in younger age groups (Lai et al. 2009) and in the future the number of workers with early-onset asthma will probably be higher than currently. Secondly, 40-year- old men are an essential part of workforce and they should generally have good work ability and be without any disabling diseases (Gould et al 2008). Thirdly, as reduced self-assessed work ability is predictive of future sick leave and disability (Ahlstrom et al. 2010, Ilmarinen et al 1997), it can be suggested that ageing of our study subjects may lead to increased absence from work and possibly shorter career.

Reduced self-estimated work ability has been connected to asthma also in earlier studies. Balder et al reported that 44% of 332 subjects with recent-onset asthma had decreased self-estimated work ability (Balder et al. 1998). In the Finnish Health 2000 Survey the mean work ability compared with lifetime best in on a scale of 0–10 was 7.1 in men with asthma and 8.0 in men without asthma ($p < 0.001$) (Gould et al 2008).

A French cohort study with a five-year follow-up showed no difference in the employment situation of working-age male asthmatics with childhood-onset asthma compared with non-asthmatics. These asthmatics worked in blue-collar jobs less often (Thaon et al. 2008). The somewhat different results in our study may indicate that choices concerning career and other selection mechanisms play different roles among French asthmatics than among the Finnish survey participants. It is noteworthy that nearly all subjects in our study currently have active asthma, while in the French study over 70% of the subjects with childhood-onset asthma were classified as having asthma only in the past. Whether these differences are due to selection processes or a different overall severity or phenotype of asthma at baseline level is difficult to judge. Other population-based studies have shown that asthma is associated with reduced employment (Blanc et al. 2001; Yelin et al. 2006).

6.2.4 The risk factors of decreased work ability

Among the asthmatics, current severe asthma, currently smoking, lower educational level and a blue collar occupation had the strongest associations with decreased work ability. Exposure to irritants, based on JEM, and self-reported occupational exposure to abnormal temperatures, was also associated with reduced work ability.

Most of the risk factors for decreased work ability that we found have also been reported previously, such as the severity of the disease (Blanc et al. 1993; Blanc et al. 1996; Balder et al. 1998; Eisner et al. 2006), smoking (Blanc et al. 2003; Eisner et al. 2006), workplace exposures to irritants (Blanc et al. 1999a; Blanc et al. 2003; Toren et al. 2009b), a blue-collar occupation (Hansen et al. 2012) and a lower educational level (Mancuso et al. 2003; Eisner et al. 2006). The lack of information on co-morbidities was a disadvantage in our study, as co-morbidities have been associated with decreased work ability among asthmatics (Hakola et al. 2011).

6.2.5 The associations between current occupational exposure and current asthma status

In *asthmatics exempted from service*, working as a manual worker/self-employed was significantly associated with asthma exacerbations and self-reported occupational exposure to asthma-aggravating factors showed a clear tendency to be associated with asthma exacerbations. In *recruits with asthma*, their current professional status and exposure had less effect on current asthma status. The ECRHS demonstrated a stronger association between occupational exposure and asthma exacerbations. The relative risk of a severe asthma exacerbation during the last year was 3.1 in participants with JEM-based occupational exposure to dust/gas/fumes (Henneberger et al. 2010). This association, which was stronger than that of our results, can be explained by the fact that the ECRHS included females and participants with adult-onset asthma, and also by the use of a different JEM.

In our study, current occupational exposure did not correlate with asthma severity. Gaga et al. reported neither associations between occupational exposure and severe asthma (Gaga et al. 2005). In another study a positive association between severe asthma and the exposure to occupational asthmogens or irritants was found among participants with adult-onset, while the authors did not detect this association among participants with childhood-onset asthma (Le Moual et al. 2005). In a Swedish study, occupational exposure to gas dust or fumes yielded an OR of 2.0 for multi-symptom asthma, which could be used as a marker of more severe asthma (Ekerljung et al. 2011).

7 CONCLUSIONS

As our study populations consisted mainly of men with early-onset atopic asthma, the conclusions cannot be generalised to other types of populations or asthma phenotypes.

Asthma is significantly milder two years after military service than during service. The short-term asthma prognosis is particularly good in subjects who suffered new-onset asthma during service. We found an association between allergic sensitisation and more severe asthma during service and after it. Asthma onset during early childhood tended to be associated with more severe asthma, but below statistical significance in this relatively small population. These prognostic factors can be useful when planning the criteria for exemption at call-up.

About half of the male conscripts suffering from different severity forms of asthma at the age of around 20 had persistent asthma approximately 20 years later. A decreased FEV_1/FVC, a decreased $FEF_{50\%}$ and a positive exercise test were associated with persistence of asthma. Over half of the subjects had a decreased $FEF_{50\%}$ as well as a positive exercise test at baseline and these parameters may be clinically meaningful prognostic measurements in males with asthma that began at a young age. The exercise test was superior to the histamine challenge in predicting the persistence of asthma, and it could be useful in evaluating long-term asthma prognosis, although further studies are needed to confirm this. Clinicians should not ignore the decreased forced expiratory flow rate at 50% of vital capacity in spirometry and a positive exercise test.

Both mild and more severe asthma at the age of around 20 seems to be associated with reduced work ability in 40-year-old males. The highest risk for decreased work ability is in asthmatics having a severe form of the disease, smoking or working in blue-collar jobs with exposure to

irritants. Therefore occupational health care professionals should pay attention to the work ability of men with asthma from youth, especially those with currently severe symptoms of the disease and support their work ability accordingly.

In middle-aged men who had relatively severe asthma at the age of around 20 current work and occupational exposure may be associated with the occurrence of asthma exacerbations. However, in men with milder asthma the role of current workplace exposure on asthma seems to be less significant. Therefore, it is advisable to take asthma severity into account in the vocational guidance of young male asthmatics. Based on our results the career restrictions seem to be unjustified for young men with relatively mild asthma. However, paying attention to the choice of future work environment and avoidance of exposure to respiratory irritants may be relevant for young men with a more severe form of asthma. These conclusions are in line with the current recommendation of the Finnish Allergy Programme.

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Asthma is an increasing health problem among the working age population and may already start at a young age. The aim was to study the asthma prognosis and the work ability of men with asthma since youth.

We used the Finnish Defence Force registers to select the study populations. Military aggravated asthma had a good 2-year and 20-year prognosis. Both mild and more severe asthma at the age of around 20 seems to be associated with reduced work ability among middle-aged men. Furthermore, current occupational exposure may be associated with asthma exacerbations among men with relatively severe asthma in youth.

Health care providers should therefore carefully follow men with asthma that began in youth, support their work ability and pay close attention to their work environment.

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Erratum:

On page 13 on line 2 the word *incidence* should be replaced with the word *prevalence.*